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Two 4-deoxy- and two 4-homopyrazofurin derivatives have been prepared via 1,3-dipolar cycloaddition reactions. These analogues have been submitted to the Army for antiviral analysis and have formed the basis of three publications submitted to the professional literature and one paper presented at a professional meeting. Synthetic methods have also been developed that can be anticipated to lead to pyrazofurin nor-amide, various pyrazofurin amides, 2-deazapyrazofurin, and 1-deazapyrazofurin during the coming year. Negotiations between Eli Lilly Company, the U.S. Army, and the University of South Florida were begun this year and are expected to lead to a supply of pyrazofurin from Lilly for this project. This will expedite the synthesis of pyrazofurin analogues with variation in the ribofuranosyl moiety.

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Stewart W. Schneller July 17, 1990
PI - Signature DATE

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Introduction

Nucleosides of 5-membered heterocycles are playing a prominent role in the design of antiviral agents.[1a] Included in this group is 4-hydroxy-3-(β-D-ribofuranosyl)pyrazole-5-carboxamide (pyrazofurin, **1**), which is a naturally occurring C-nucleoside that shows significant broad spectrum *in vitro* antiviral activity against DNA and RNA viruses.[1b,1c] The extent of its antiviral properties is represented by its activity against pox-, picorna, toga-, myxo-, rhabdo-, arena-, and bunyaviruses[1d-1f] with a high degree of selectivity

Even with its promising activity and broad safety margin in cell cultures, there have been reports[1e,1g] that the toxicity of **1** may[1h] limit its usefulness as an antiviral agent. However, De Clercq and Torrence[1d] have suggested that the toxicity of **1** is unlikely to be associated with the structural components that are responsible for its antiviral properties. To evaluate this suggestion for the proposes of producing non-toxic pyrazofurin-derived agents that are effective against the virus groups mentioned above, a systematic structure-antiviral activity study is being done under this contract. There is no literature precedent for this approach with **1** as an antiviral agent.

To accomplish the proposed plan, the heterocyclic unit, ring hydroxyl, amide side chain, and ribofuranosyl center of **1** are being sythetically varied. Following the syntheses, the target analogues are being submitted to the USAMRIID for antiviral analyses

During this reporting period, synthesis of the following analogues has been pursued: (i) 4-deoxypyrazofurin (**2**) and its acyclic derivative (**3**), (ii) 4-homopyrazofurin (**4**) and its acyclic derivative (**5**), (iii) the pyrazofurin nor-amide (**6**), (iv) pyrazofurin amides (**7**), (v) 2-deazapyrazofurin (**8**), and (vi) 1-deazapyrazofurin (**9**). The preparation of **2-5** and progress towards **6-9** are reported herein.

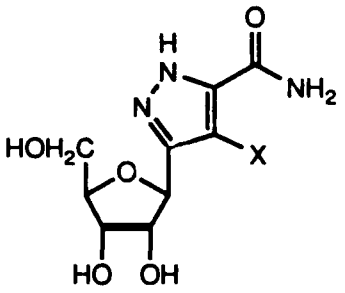
Body

1. Synthesis of 4-Deoxypyrazofurin (2)

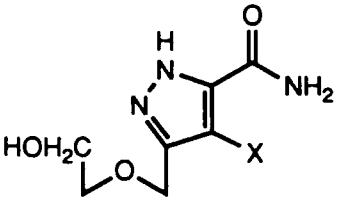
A review of the literature revealed two syntheses of 4-deoxypyrazofurin (**2**).[2] Both of these routes were quite tedious and, as a consequence, inconvenient for the goals of this laboratory. Thus, a new route to **2** was sought and has been achieved in a ten step process with an overall yield of 17%.

The retrosynthetic analysis shown in Scheme 1 indicated that **2** would be readily available from commercial starting materials (**11** and **13**). To pursue Scheme 1, the diazoribofuranose derivative **10** was required for the 1,3-dipolar cycloaddition reaction with methyl propiolate (**11**). Compound **10** has been reported[3] from 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonitrile (**12**, Scheme 2); however, various modifications of this route[3] to **10** were necessary to improve the overall efficiency of the synthesis of **2**.

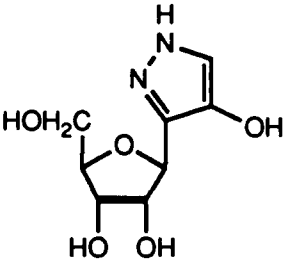
The customary method for preparing **12**[4] (method a, Scheme 2), which involves treating 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**13**, Scheme 2) first with hydrogen bromide followed by mercuric cyanide, was found to be laborious and time consuming and the removal of the mercury salts from the crude product was often incomplete, resulting in only moderate yields of **12** (50-60%). In view of the cyanation of S_N1-active compounds with trimethylsilyl cyanide (TMSCN) in the presence of a Lewis acid,[5] **13** was subjected to these conditions (method b, Scheme 2). This resulted in an 80%



1, X=OH
2, X=H
4, X=CH_2OH



3, X=H
5, X=CH_2OH



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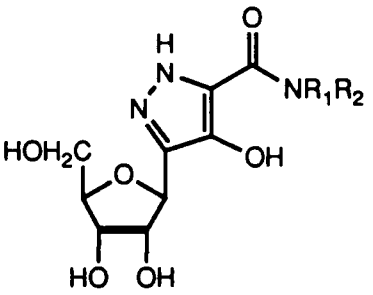
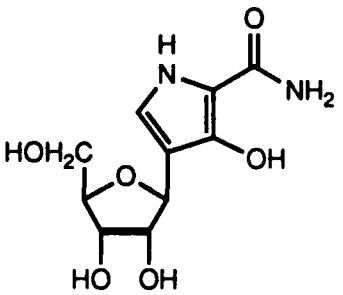


7, R_1=H, alkyl or aryl
R_2=alkyl or aryl



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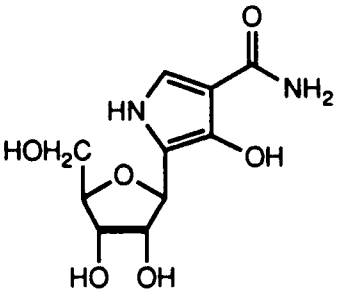

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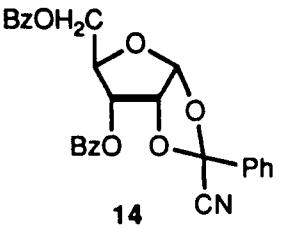
yield of crystalline **12**, which was identical (spectroscopically, chromatographically) to **12** prepared by method a.

Two interesting observations were made during the investigations leading to the preparation of **12** by method b of Scheme 2. First, not surprisingly, it was found that a 2'-*O*-ester group (for example, benzoyl) was necessary for the stereospecific introduction of the cyano group. Second, at low temperature, four compounds were isolated from the reaction including **12**, **13**, and the intermediate cyanoketals **14** and **15**. The latter two products were substantiated by ^{13}C NMR spectral analysis that showed the appearance of (i) nitrile carbons (δ 117.1 and 116.3) different from the nitrile carbon of **12** (δ 115.83) and (ii) carbons (δ 105.65, 104.60, 101.86, and 100.40) attributable to the anomeric carbon and the cyano bearing carbon for each intermediate.



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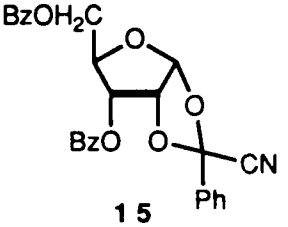

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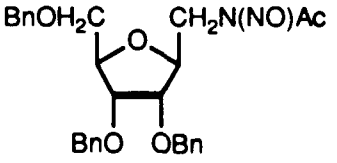
The diastereomeric intermediates **14** and **15** were converted to **12** when subjected to the reaction conditions of method b of Scheme 2. With this observation, the standard mechanistic rationalization of Scheme 3 depicts the likely steps leading from **13** to **12** with TMSCN.

With **12** available it became necessary to convert it to the diazo derivative **10** (for use in Scheme 1). A literature method[4] for accomplishing this via an N-nitrosourea derivative afforded low yields and was found too tedious to perform on the scale desired. Thus, an alternative method was sought that led to developing the preparation of **10** from the N-nitrosoamide **16**.[3] In this direction, reduction of nitrile **12** required the use of a reagent that would not cleave the benzoyl protecting groups. The use of sodium trifluoroacetoxyborohydride[6] allowed this transformation yielding 1-amino-2,5-anhydro-3,4,6-tri-*O*-benzoyl-1-deoxy-**D**-allitol (**17**, Scheme 4), which was converted to 1-acetamido-2,5-anhydro-3,4,6-tri-*O*-benzoyl-1-deoxy-**D**-allitol (**18**) upon treatment with acetic anhydride/triethylamine.



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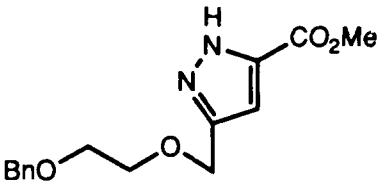
At this point in the synthesis it became apparent that the benzoyl protecting groups of **18**, which were needed for the selective synthesis of **12** (method b, Scheme 2), would not survive the later basic conditions needed to form **10**. Thus, **18** was first reacted with sodium methoxide to remove the benzoyl groups and this was followed by reprotection with benzyl chloride at 15 °C to give **19** (Scheme 4). It was critical that the temperature of the benzylation reaction did not exceed 15 °C since higher temperatures resulted in N-benzylation of the amide functionality.

Treatment of **19** with dinitrogen tetroxide/acetic acid at 3 °C easily provided the N-nitrosoamide **16**, which was treated directly with a well stirred mixture of aqueous potassium hydroxide/diethyl ether to generate the diazo dipole **10**. Reaction of **10** (Scheme 5) with methyl propiolate resulted in the pyrazole nucleoside **20** as the only detectable regioisomer. This structural assignment was based on the ^{1}H and ^{13}C NMR analysis in which the ^{1}H shift of 6.61 ppm observed for the pyrazole proton and the ^{13}C resonance for the unsubstituted pyrazole carbon at 104.94 ppm correlated well with the data for **22** adequately established in the next Section of this report.



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Exposure of **20** to methanolic ammonia at 110 °C resulted in the formation of amide **21**. Deprotection of **21** by transfer hydrogenation with $PdO{\cdot}H_2O$/cyclohexene resulted in the formation of the desired 4-deoxypyrazofurin (**2**).

2. Synthesis of Acyclo 4-Deoxypyrazofurin (3)

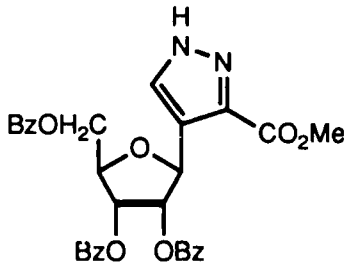
Analogous to the synthesis of **2**, **3** (Scheme 6) was foreseen as available from the protected pyrazole ester **22**, which was, in turn, to be prepared via the regiospecific[7] 1,3-dipolar cycloaddition of the previously unknown diazoalkane **23** and methyl propiolate. To accomplish this task, the preparation of **23** became the initial synthetic goal.

The results of previous synthetic efforts in our laboratory towards target **2**, and the laboratories of others,[8] indicated that the diazo functionality of **23** could be readily prepared from the corresponding nitrile. A search of the literature[9,10] revealed that a desirable nitrile precursor (that is, **24** of Scheme 6) could be prepared via the Lewis acid catalyzed reaction of trimethylsilyl cyanide (compare to Scheme 2) and 1,3-dioxolane (Scheme 6). This was achieved to give **24** using zinc iodide as the catalyst. Since the trimethylsilyl protecting group was not expected to withstand the subsequent conditions required for preparation of the diazoalkane, it was removed by treatment with citric acid in methanol and the resultant alcohol **25** was reprotected as the benzyl ether **26** by treatment with sodium hydride followed by benzyl bromide. Following the procedures leading to **10**, the nitrile moiety of **26** was reduced efficiently with lithium aluminum hydride to yield the corresponding amine, which was directly converted to amide **27** with acetic anhydride/triethylamine in diethyl ether. Dinitrogen tetroxide was then utilized to convert amide **27** into its *N*-nitroso derivative **28**. The desired diazoalkane dipole **23** was obtained by exposure of **28** to aqueous potassium hydroxide.

With **23** available, its cycloaddition with methyl propiolate proceeded cleanly to give pyrazole **22** as the only detectable regioisomer. The conversion of ester **22** to amide **29** was accomplished by treatment with ammonia in methanol in a sealed glass tube. Deprotection of **29** using palladium oxide/cyclohexene[11] in refluxing ethanol afforded the title compound **3**.

The regiochemistry of the cycloaddition reaction was confirmed by examination of the ^{1}H and ^{13}C NMR spectra of pyrazole **22**. It has been shown that the chemical shifts of H-3, H-4 and H-5 of the pyrazole ring fall in characteristic regions.[12] Specifically, H-3 and/or H-5 of alkyl and/or acyl substituted pyrazoles tend to exhibit chemical shifts downfield of 7.25 ppm, whereas H-4 tends to appear upfield of 7.0 ppm. The pyrazole ring proton of the cycloadduct exhibited a chemical shift of 6.76 ppm, falling well within the range described for H-4 in pyrazole ring systems. Additionally, the shift observed for **22** is consistent with the chemical shift of 6.63 ppm reported[2b] for H-4 of **2**.

This trend was further supported by comparison with the ^{1}H NMR data reported for methyl 4-(2,3,5-tri-*O*-benzoyl-β-**D**-ribofuranosyl)pyrazole-3(5)-carboxylate[13] (**30**, drawn below, where C-5 is unsubstituted and C-4 is substituted) in which H-5 exhibited a shift of 7.87 ppm that is in the region expected.[12]. The ^{13}C spectra provided additional evidence since a heteronuclear coupling experiment performed on **22** showed that the carbon atom at 107.18 ppm was bonded to a hydrogen. The chemical shift for this carbon is similar to that observed for C-4 (104.51 ppm) in pyrazole.[14]



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3. Synthesis of 4-Homopyrazofurin (4) and Acyclo 4-Homopyrazofurin (5)

Scheme 7 presents the retrosynthetic perspective through a 1,3-dipolar cycloaddition reaction (**10** + **30**) upon which the preparation of **4** and, in turn, **5** was designed. Since a convenient synthesis of **10** was described in Scheme 4, it remained to develop a route to the unknown dipolarophile **30**, which is shown in Scheme 8.

Subjecting the monobenzyl ether of ethylene glycol (**31**)[10] to a Swern oxidation[15] yielded aldehyde (**32**), which was homologated to the *geminal* dibromoalkene **33** by treatment with a reagent prepared from the reaction of carbon tetrabromide with triphenylphosphine.[16] Treatment of **33** with *n*-butyllithium resulted in a 1,2-elimination to a bromoalkyne intermediate that then underwent metal-halogen exchange to the terminal alkyne anion that was trapped[19] with methyl chloroformate to give **30**.

Reaction of **30** with **10**, which was generated as needed from 1-acetamido-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-**D**-allitol (**19**), proceeded cleanly to yield one detectable regioisomer (**34**, Scheme 9). The regiochemistry of this cycloaddition was determined by comparing the ^{13}C NMR chemical shift for C-4 of **34** (116.51 ppm) with the same carbon of the 4-deoxypyrazofurin ester **20** (104.94 ppm), which is in agreement with the expected downfield shift (typically 10-15 ppm) that results when an aromatic proton is replaced by a $-CH_2O-$ group.[18]

Amidation of ester **34** with ammonia saturated methanol yielded the amide **35**, which was fully deprotected utilizing transfer hydrogenation to provide the desired **4**.

A similar sequence of reactions (Scheme 10) was employed to prepare the acyclic analogue **5**. The regiochemistry of the cycloaddition reaction that produced **36** was also confirmed using ^{13}C NMR data in which C-4 for **36** showed the same downfield shift trend when compared to **22** (that is, 118.26 ppm for **36** *versus* 107.18 ppm for **22**) as described herein for **34** relative to **20**.

4. Synthesis of Pyrazofurin Nor-Amide (6)

The initial plan to **6** (Scheme 11) was to employ the 1,3-dipolar cycloaddition reaction of **10** with benzyloxyacetylene (**38**), which was expected to proceed[19] with the correct regiochemistry to give **39**. Compound **38** had been reported in the literature[20] via the reactions shown in Scheme 12. However, our attempts to repeat this preparation led to the formation of benzylamine and benzyl acetate (**41**) and recovery of starting material (Scheme 12). The mechanism for this result is also given in Scheme 12 and takes into account the anhydrous conditions used that precludes the formation of **38** and its hydration to **41**.

Thus, with this result in hand, the bromo analogue of **40** was more conveniently prepared as shown in Scheme 13 and treated with sodium in liquid ammonia. In this case, benzylamine, benzyl alcohol and bromoacetaldehyde resulted. A proposed mechanism for the formation of these products is given in Scheme 13 that suggests that **43** is not first converted to the dibenzyl ketenal **42** of Scheme 12 but that the products result directly from the starting bromo compound.

The non-nucleophilic base sodium hydride and the sterically congested base potassium *t*-butoxide gave results similar to those of Schemes 12 and 13.

An interesting lead did arise when **43** was treated with lithium in diisopropylamine to give a mixture of (Z)- and (E)-1-benzyloxy-2-bromoethene (**44** and **45**, respectively, in Scheme 14). Reaction of **45** with sodium amide, under the literature conditions[20] for preparing **38**, formed the isoindanone **46**. This product was postulated as having arisen from the desired benzyloxyacetylene via the rearrangement shown in Scheme 14. Thus, by lowering the temperature of the sodium/liquid ammonia reaction to -42°C for a very short period of time, it has been possible to isolate **38** in 20% yield.

Plans are now to react **38** with **10** as proposed in Scheme 11. Debenzylation of the resultant **39** with palladium oxide (see Scheme 5 or 9) will provide **6**.

Also, interestingly, the product from reaction of **45** with sodium/liquid ammonia at low temperature could be trapped with methyl chloroformate to give the alkyne ester **47** (Scheme 15). A dipolar cycloaddition reaction of **47** with **10** can be expected to give, following amidation and debenzylation, an efficient synthesis of pyrazofurin that would not require separation of the α and β anomers. At this point, it should also be noted that **47** is critical to the proposed preparation of 1-deazapyrazofurin presented in Scheme 28.

Efforts to improve the yield of the (Z)-isomer **44** (which would allow for a trans elimination of hydrogen bromide and be more useful than **45** in Scheme 14) by following a literature[21] procedure used to prepare the *t*-butoxy derivative **48** (path a, Scheme 16) led to retention of the ethoxy group (path b, Scheme 16) rather than the benzyloxy moiety when

benzyl alcohol was used in the sequence in place of *t*-butyl alcohol. Use of the phosphorus pentachloride/triethylamine conditions with **43** (whereby ethoxy could not be preferentially lost) produced bromoacetaldehyde and benzyl chloride (Scheme 16). A proposed mechanism for the formation of these latter two products is shown as part of Scheme 16.

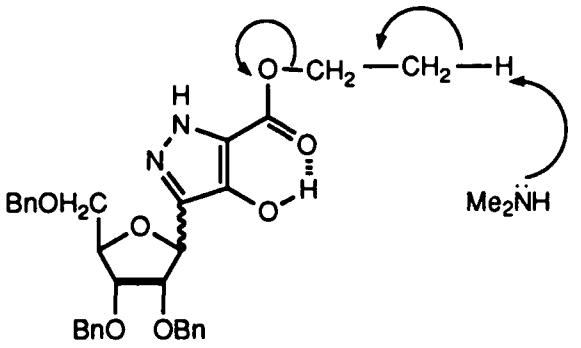
If the method proposed in Scheme 11 fails to give **6**, two alternative pathways are in mind. The first begins with the dipolar cycloaddition reaction of dibenzyl ketenal (**42**)[22] and **10** that can be expected[19] to give the desired regioisomer **50**. Debenzylation of **50** followed by the loss of water will result in **51**, which is the keto tautomer of **6** (Scheme 17).

The second means to **6** could begin with **52**, whose synthesis is described in Scheme 18, and follow a path of saponification[23]/decarboxylation[23]/debenzylation and anomer separation.

5. Synthesis of Pyrazofurin Amides (7)

The route to the amide derivatives explored during the reporting period is outlined in Scheme 18, which employs a literature preparation[24] of the ester **52**. As shown in Scheme 20, reaction of α/β mixture of **52** with methylamine in methanol at room temperature in a sealed vessel gave an α/β mixture of the desired amide **58** whereas reaction at 100°C gave only the β isomer **58**. The observation of epimerization to only one anomer under these latter reaction conditions is not surprising in view of a similar result reported by Karagiri[24] when morpholine was the amine. Interestingly, when we treated α/β-**52** with morpholine under the Karagiri conditions,[24] no reaction occurred.

Use of other amines led to less successful results than with methylamine. For example, reaction of α/β-**52** with dimethylamine gave the β-anomer of the carboxylic acid **59** (whose proposed non-aqueous mechanism of formation is shown below). Also, treatment of α/β-**52** with cyclohexylamine in methanol led to transesterified **60** and no reaction took place (as with morpholine) when aniline neat or in benzene was used.



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Attention then turned to the possibility that the 4-hydroxyl substituent may have been interfering with the amidation of the ester functionality of α/β-**52**. To evaluate this possibility, α/β-**52** was treated with one equivalent of benzyl bromide and found to give the dibenzyl product **61** (Scheme 21) and unreacted starting material, contrary to the report of Robins[25] in which only the 4-benzyloxy product formed with slightly more than one equivalent of benzyl bromide. (It should be noted that the site of N-benzylation in **61** has not been unambiguously assigned.)

Reaction of **61** with dimethylamine in methanol and cyclohexylamine neat at elevated temperatures has given the β-anomer of the desired amides (**62** and **63**). The β configuration for **62** and **63** has been assigned by analogy to the report of Karagiri and co-workers[24] for the product of **52** with morpholine.

Debenzylation of β-**58** (Scheme 22) under atmospheric hydrogenation using platinum on carbon has provided **7a**, which will be submitted shortly to the Army for testing. At this time, similar debenzylation of **62** has caused some difficulty in achieving complete debenzylation of the ring nitrogen site. This is being investigated.

6. Synthesis of 2-Deazapyrazofurin (8)

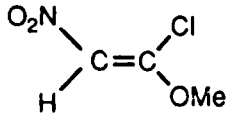
The first approach considered to **8** sought the 1,3-dipolar cycloaddition reaction between the ketene **64** and commercially available methyl isocyanoacetate (**65**) as illustrated in Scheme 23. Steps *c-e* failed to give the desired product, resulting in what appears to be a material arising from addition of the dipole **65** to the carbonyl of the ketene (to give an oxazole homonucleoside)[26] rather than the carbon-carbon double bond.

Attention to seeking **8** has more recently focused on the plan shown in Scheme 24. In this regard, reaction of **66** with sodium hydride foliowed by methyl formate gave tne anticipated complex mixture of four products (**67**, α/β anomers with syn/anti hydroxyl orientations) that could not be separated. Reaction of this mixture with ethyl glycinate gave a similar mixture of the enamine **68**. Attempts to ring close **68** with various bases failed. Believing that the free NH of **68** may b: interfering with its base promoted ring closure, efforts are currently underway to treat **67** with ethyl N-benzylglycinate and to pursue ring closure of the resultant N-protected product.

An alternative route to **8** is shown in Scheme 25 and will be considered if the modification using ethyl N-benzylglycinate in Scheme 24 is unfruitful.

7. Synthesis of 1-Deazapyrazofurin (9)

The two initial plans considered to **9** are given in Schemes 26 and 27. Difficulties in preparing the requisite Wittig reagent in Scheme 26 and the phosphonium salt **70** in Scheme 27 led to abandonment of these routes. In the latter case (Scheme 27) reaction of **69** with triphenylphosphine led to triphenylphosphine oxide and, possibly, **71** rather than **70**.



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The synthesis of **9** now being considered is shown in Scheme 28 and awaits the availability of **47** described in Scheme 15.

Conclusions

The first year of this contract has seen the successful synthesis of four pyrazofurin derivatives (**2-5**), which have been submitted to the Army for antiviral analysis. Also, synthetic methods have been developed that will allow entry into (i) the pyrazofurin nor-amide (**6**), (ii) pyrazofurin amides (**7**), (iii) 2-deazapyrazofurin (**8**), and (iv) 1-

deazapyrazofurin (**9**). In this regard, the coming year will see variations in Schemes 11 (**6**), 21/22 (**7**), 24/25 (**8**) and 28 (**9**) pursued. In doing so, (i) conditions for improved yields of **38** will be sought, (ii) a convenient N-debenzylation will be established for use on derivatives **62** and **63** and related amides (Scheme 21), and (iii) an N-substituted derivative of **68** will be necessary for fruitful ring closure of **68** in Scheme 24. Based on the exploratory work presented herein, success to **6-9** can be confidently predicted.

It is appropriate to note at this point that negotiations between Eli Lilly Company, the U.S. Army, and the University of South Florida, which were begun this year, are expected to produce a sizeable quantity of pyrazofurin from Lilly for this project. If this plan materializes, the contributed pyrazofurin will be used to prepare derivatives with structural variation in the ribofuranosyl moiety as outlined in the original proposal. If pyrazofurin does not become available from Lilly for preparing these latter analogues, it will be made by Scheme 15 or by employing ammonia (instead of an organic amine) in Scheme 18

To date, three papers have been submitted to the professional literature for publication and one paper has been presented at a professional meeting based on work supported by this contract.

Experimental

Materials and Methods. Melting points were recorded on a Mel-Temp capillary melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. IR spectra were recorded on a Beckman Model FT 1100 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 MHz and 22.5 MHz, respectively) in $CDCl_3$ or DMSO-d_6 referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck Silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. The column chromatographic purifications were performed using Davidson Chemical silica gel (60-200 mesh) or Aldrich silica gel (230-400 mesh, 60 Å) eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

2,5-Anhydro-3,4,6-(tri-*O*-benzoyl)-D-allonitrile (12). Commercially available (Aldrich) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-**D**-ribofuranose (**13**)(20 g, 39.64 mmol) was dissolved in 100 mL of dry CH_2Cl_2 under N_2 in a oven dried flask equipped with gas inlet, condenser, septum, and gas bubbler. The solution was then treated with 6.3 mL of trimethylsilyl cyanide[31] (47.6 mmol) and 2.6 g of anhydrous $SnCl_4$ (10 mmol) and the mixture heated to reflux temperature for 4 h under N_2. After the mixture cooled, it was poured carefully over 200 mL of ice/H_2O. The aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL) and the combined organic extracts washed with 5% aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated by rotary evaporation. The resulting brown syrup was purified by flash chromatography (CH_2Cl_2) yielding a white solid, which was further purified by recrystallization from absolute EtOH to give **12** (15.95 g, 80%) as long white needles which were identical to a sample prepared by the literature procedure[4]: mp 78-80 °C (EtOH) (lit.[4] mp 78-80 °C); R_f=0.39 (hexane:EtOAc, 70:30); IR (neat, cm^{-1}) 1720 (CO); ^1H NMR ($CDCl_3$) δ 8.05-6.96 (m, 15 H, Ar), 5.91-5.55 (m, 2 H), 4.86 (d, J= 9 Hz, 1 H), 4.63 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.15, 165.12, 164.91, 133.97, 133.81, 133.43, 129.86, 129.31, 128.56, 128.23, 115.83, 80.94, 74.54, 71.94, 69.51, 63.22.

1-Amino-2,5-anhydro-3,4,6-tri-*O*-benzoyl-1-deoxy-D-allitol (17). A solution of sodium trifluoroacetoxyborohydride (59 mmol) was prepared by adding 6.8 g (59 mmol) of trifluoroacetic acid dropwise, under N_2, to an ice bath cooled, stirred suspension of $NaBH_4$ (2.4 g, 63 mmol) in 10 mL of dry THF. A solution of 20 g (42.2 mmol) of **12** in 30 mL dry THF was added dropwise, under N_2, to the reducing agent and the reaction stirred at 27 °C for 18 h. After this period of time, the reaction was cooled in an ice/H_2O bath and quenched with 2 mL of H_2O. The mixture was then concentrated *in vacuo* and the resulting white paste partitioned between 200 mL of CH_2Cl_2 and 200 mL of H_2O. The organic layer was separated, washed with H_2O (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield crude **17** as a yellow syrup, which was used directly in the preparation of **18** without further purification.

1-Acetamido-2,5-anhydro-3,4,6-tri-*O*-benzoyl-1-deoxy-D-allitol (18). The yellow syrup obtained above (**17**) was dissolved in 100 mL of dry THF and

treated with Et_3N (5.16 g, 51 mmol), acetic anhydride (4.76 g, 46.6 mmol), and 4-dimethylaminopyridine (0.01 g). The reaction mixture was stirred at 25 °C for 18 h. After this period, the reaction was cooled to 0 °C and quenched with MeOH (1.5 g, 46.8 mmol). The mixture was then concentrated *in vacuo* and the resulting light brown syrup dissolved in benzene (200 mL). The benzene solution was washed with 1 *N* HCl (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a light yellow syrup. This syrup was purified by silica gel chromatography (EtOAc:hexane, 1:1) to yield 12.1 g of **18** (57% from **12**): R_f=0.4 (EtOAc:benzene, 1:1); IR (neat, cm^{-1}) 3311 (NH), 1730 (ester CO), 1653 (amide CO); ^1H NMR ($CDCl_3$) δ 8.1-7.3 (m, 15 H, Ar), 5.7 (m, 1 H), 5.2-4.9 (m, 2 H), 4.5 (m, 4 H), 2.0 (m, 2 H), 1.85 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.0, 166.3, 165.5, 164.7, 133.6, 133.4, 129.2, 128.9, 128.7, 80.6, 79.5, 72.3, 72.7, 64.0, 40.4, 22.9. Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; N, 2.71. Found: C, 67.12; H, 5.28; N, 2.67.

1-Acetamido-2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-D-allitol (19). A solution of 2.6 g (5 mmol) of **18** in 20 mL of dried MeOH was treated with 4.1 g of a 20% NaOMe/MeOH solution (15 mmol NaOMe) and the mixture heated to reflux for 45 min under the protection of a drying tube. Following this, the reaction mixture was cooled to room temperature, quenched with 1.49 g of conc. HCl (15 mmol HCl) and concentrated *in vacuo*. The remaining syrup was dissolved in 50 mL of H_2O, and the aqueous phase washed with CH_2Cl_2 (2 x 25 mL). The aqueous layer was concentrated *in vacuo*; the residue was dissolved in 100 mL of absolute EtOH, filtered, and concentrated *in vacuo* to afford a yellow syrup. This syrup was dissolved in 10 mL of anhydrous DMSO, transferred to a three neck flask and treated, under N_2, with solid KOH (1 g, 15.1 mmol). The reaction mixture was then cooled to 15 °C and benzyl chloride (2.11 g, 16.7 mmol) added dropwise with the aid of mechanical stirring. The temperature was maintained at 15 °C for 2 h. After this period, the reaction was poured over 100 mL of ice/H_2O and the mixture stirred for 1 h. The aqueous phase was then extracted with benzene (3 x 75 mL), and the combined organic extracts dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a colorless syrup. This syrup was purified by silica gel chromatography (benzene:EtOAc, 1:1) to afford 1.3 g (55%) of **19** as a white solid: R_f = 0.2 (benzene:EtOAc, 1:1); mp 68 °C (lit.[3] mp 65-68 °C); IR (KBr, cm^{-1}) 3316 (NH), 1658 (amide I); ^1H NMR ($CDCl_3$) δ 7.34 (s, 15 H, Ar), 6.20 (br s, 1 H, NH), 4.52 (s, 6 H, benzyl CH_2), 4.0-3.5 (m, 8 H) 1.54 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.52, 139.12, 139.01, 129.91, 129.80, 129.42, 129.26, 82.45, 82.02, 79.85, 78.61, 74.98, 73.68, 73.41, 71.35, 22.43. Anal. Calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 73.13; H, 6.97; N, 2.93.[32]

Methyl 3(5)-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-carboxylate (20). A mixture composed of **19** (1.2 g, 2.5 mmol) dissolved in 20 mL of a 1:1 mixture of CCl_4:glacial AcOH containing 1.2 g of anhydrous AcONa was cooled to 3 °C in an ice/H_2O bath, treated with 2 mL of liquid N_2O_4, and then stirred for 1.5 h at 3 °C. Following this period, the solution was poured over 120 mL of ice/H_2O with subsequent vigorous stirring of the resultant mixture for 0.5 h. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to yield 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-nitrosoacetamido-**D**-allitol (**16**) as a light green syrup: IR (neat, cm^{-1})

1733 (CO), 1500 (NO). This syrup, which showed no IR absorption at 3311 cm^{-1} (NH) or 1658 cm^{-1} (CO) to suggest unreacted **19**, was used immediately in the next reaction.

The *N*-nitroso amide **16** (assumed to be 2.5 mmol) was dissolved in 6 mL of Et_2O and mixed vigorously with an ice cold solution of 1.44 g of KOH dissolved in 3 mL of H_2O. The mixture was then stirred at 3 °C for 45 min after which the IR spectrum of the ether layer showed the formation of a strong band at 2067 cm^{-1} (CHN_2) and with no band at 1500 cm^{-1} (NO) apparent. The reaction mixture was diluted with Et_2O (12 mL) and H_2O (25 mL) and the layers separated. The Et_2O layer was washed with H_2O (10 mL) and dried rapidly by first swirling the ether phase over KOH pellets and followed by decantation into anhydrous $MgSO_4$. After filtration, the golden colored filtrate containing 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diazo-**D**-allitol (**10**), which displayed an IR band (neat, cm^{-1}) at 2067 (N_2), was used immediately in the next reaction.

The aforementioned ethereal solution of **10** was added to a solution of 0.25 g (3 mmol) of methyl propiolate (**11**) in 10 mL of anhydrous Et_2O. The mixture was stirred at 27 °C for 16 h after which TLC analysis (EtOAc:hexane, 1:1) indicated that the reaction had proceeded to completion (during this time, the solution color changed from golden to light yellow). The reaction mixture was then concentrated *in vacuo* and the residue purified by column chromatography (EtOAc:hexane, 1:1) yielding **20** (1.01 g, 76% from **19**) as a colorless syrup: R_f = 0.33 (EtOAc:hexane, 75:25); IR (neat, cm^{-1}) 3250, 3050, 2900, 1725, 1450, 1230, 1100, 750, 700; ^1H NMR ($CDCl_3$) δ 13.0 (br s, 1 H, pyrazole NH), 7.30 (s, 15 H, ArH), 6.61 (s, 1 H, pyrazole H-4), 5.21 (d, J=3.1 Hz, 1 H, H-1'), 4.6-3.58 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 162.42, 145.78, 142.75, 137.49, 137.33, 137.06, 128.61, 128.50, 128.39, 128.01, 127.91, 104.94, 81.86, 80.50, 76.82, 76.71, 73.41, 72.38, 68.42, 51.95. Anal. Calcd for $C_{31}H_{32}N_2O_6$: C, 70.43; H, 6.10; N, 5.30. Found: C, 70.23; H, 6.12; N, 5.30.

3(5)-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-carboxamide (21). A solution of **20** (700 mg, 1.32 mmol) in 30 mL of freshly distilled MeOH was saturated with NH_3 at 3 °C and the resulting mixture heated in a sealed glass tube at 110 °C for 16 h. Upon cooling, TLC analysis ($CHCl_3$:MeOH, 9:1) indicated that the reaction had proceeded to completion. The solution was then concentrated *in vacuo* and the residue purified by silica gel column chromatography ($CHCl_3$:MeOH, 9:1) giving **21** (650 mg, 95%) as a colorless glass: R_f=0.57 ($CHCl_3$:MeOH, 9:1); IR (neat, cm^{-1}) 3480, 3350, 3200, 2900, 1680, 1600, 1500, 1450, 1100, 1033, 750, 700; ^1H NMR ($CDCl_3$) δ 11.78 (br s, 1 H, pyrazole NH), 7.31 (s, 15 H, ArH), 6.57 (s, 1 H, pyrazole H-4), 6.04 (br d, 2 H, NH_2), 5.24 (d, J=3 Hz, 1 H, H-1'), 4.63-3.54 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 164.31, 146.81, 144.65, 137.44, 137.17, 136.95, 128.61, 128.50, 128.39, 128.07, 127.96, 127.85, 102.55, 81.58, 80.18, 76.82, 76.34, 73.57, 72.32, 68.58. Anal. Calcd for $C_{30}H_{31}N_3O_5$: C, 70.16; H, 6.08; N, 8.18. Found: C, 70.14; H, 6.23; N, 8.14.

3(5)-(β-D-Ribofuranosyl)pyrazole-5(3)-carboxamide (4-Deoxypyrazofurin, 2). A solution of **21** (630 mg, 1.23 mmol) in 20 mL of a 3:1 mixture of absolute EtOH:cyclohexene was treated with 50 mg of palladium(II) oxide hydrate. The mixture was refluxed for 1 h after which TLC analysis (MeCN:H2O, 96:4) showed complete loss of starting material. The reaction mixture was then cooled, filtered through a pad of celite that had been washed with hot EtOH; the celite pad was then washed with hot EtOH, and the combined filtrates concentrated. The resulting colorless glass was purified by column chromatography using silica gel (MeCN:H_2O, 94:6) to yield **2** (280 mg, 94%)

as a white amorphous solid; R_f = 0.29 (MeCN:H_2O, 94:6); IR (KBr, cm^{-1}) 3500-3200, 2920, 1670, 1600; ^1H NMR (DMSO-d_6) δ 7.5 (br d, 2 H, NH_2), 6.75 (s, 1 H, H-4), 4.80-3.53 (m, 9 H); ^{13}C NMR (DMSO-d_6) δ 162.42, 146.65, 143.56, 103.47, 84.78, 76.66, 75.68, 71.02, 61.81; Anal. Calcd for $C_9H_{13}N_3O_5$ • 0.5 MeOH • 0.25 H_2O: C, 43.26; H, 5.92; N, 15.93; Found: C, 43.24; H, 5.73; N, 15.93.[33]

5-(Trimethylsiloxy)-3-oxapentanenitrile (24).[10] A mixture of freshly distilled 1,3-dioxolane (15.41 g, 208 mmol), freshly prepared trimethylsilyl cyanide[31] (20.64 g, 200 mmol), and anhydrous ZnI_2 (500 mg) was stirred under N_2 at 27 °C in an oven dried flask. The reaction mixture slowly became yellow and aliquots were taken to follow the course of the reaction by ^1H NMR spectroscopy. When the reaction was complete (48 h), a distillation head was attached to the reaction vessel and the product distilled directly, yielding **24** (22.1 g, 61%) as a clear, colorless liquid: bp 79-81 °C at 1 torr (lit.[10] bp 40-45 °C at 0.4 torr); IR (neat, cm^{-1}) 2960, 2870, 1466, 1433, 1250, 1140, 1100, 950, 850; ^1H NMR ($CDCl_3$) δ 4.39 (s, 2 H, CH_2), 3.73 (m, 4 H, CH_2CH_2), 0.10 (s, 9 H, $SiMe_3$); ^{13}C NMR ($CDCl_3$) δ 115.90, 74.39, 60.83, 56.43, 4.78 ppm;. Anal. Calcd for $C_7H_{15}NO_2Si$: C, 48.52; H, 8.73; N, 8.08; Found: C, 48.31; H, 8.39; N, 7.81.

5-Hydroxy-3-oxapentanenitrile (25).[10] To a stirred solution of citric acid monohydrate (2.83 g, 14.74 mmol) in 150 mL of MeOH was added 14.3 g (82.6 mmol) of **24**. After 30 min, the solution was neutralized with saturated K_2CO_3 solution and the volume of the solution reduced by ca. 50% *in vacuo*. The resultant solution was then diluted with 115 mL of saturated brine and extracted with 10% 2-propanol/$CHCl_3$ (4 x 170 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate evaporated *in vacuo* to give a light yellow liquid. The liquid was distilled using a Kugelrohr apparatus to give **25** (6.75 g, 81%) as a clear, colorless liquid: bp 94-96 °C at 1 torr (lit.[10] bp 55 °C at 0.1 torr); IR (neat, cm^{-1}) 3400, 2933, 2880, 2250, 1450, 1360, 1115, 1080, 895; ^1H NMR ($CDCl_3$) δ 4.35 (s, 2 H, CH_2), 3.73 (m, 4 H, CH_2CH_2), 3.17 (br s, 1 H, D_2O exch, OH); ^{13}C NMR ($CDCl_3$) δ 115.90, 72.67, 60.97, 56.36 ppm; Anal. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.85; Found: C, 47.20; H, 6.99; N, 13.55.

5-(Benzyloxy)-3-oxapentanenitrile (26).[10] A solution composed of **25** (3.46 g, 34.3 mmol) dissolved in 20 mL of DMF was added dropwise under Ar to a stirred slurry of 97% NaH (1 g, 40.4 mmol) in 25 mL of DMF cooled to 3 °C in an oven dried flask. Upon completion of the addition, the reaction was allowed to warm to 27 °C and the stirring continued for 30 min. After this period of time, the reaction mixture was recooled to 3 °C and 7 g (41 mmol) of benzyl bromide added dropwise. The reaction mixture was allowed to warm to 27 °C and the stirring continued for 6 h. The mixture was then cooled to 3 °C and 1 mL of H_2O added dropwise to quench the reaction. The reaction mixture was allowed to warm to 27 °C and stirring was continued for 0.5 h. The mixture was partitioned between 100 mL of H_2O and 100 mL benzene, the benzene layer was collected and the aqueous layer further extracted with benzene (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to give a brown syrup. The crude syrup was purified using a Kugelrohr distillation apparatus to yield pure **26** (3.9 g, 60%) as a clear, colorless syrup: bp 140 °C at 1 torr (lit.[10] bp 100 °C at 0.25 torr); IR (neat, cm^{-1}) 3080, 3030, 2920, 2880, 2250, 1468, 1360, 1105, 890, 740, 700; ^1H NMR ($CDCl_3$) δ 7.31 (s, 5 H, ArH), 4.53 (s, 2 H, benzyl CH_2), 4.25 (s, 2 H, OCH_2CN), 3.66 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 137.82, 128.45, 127.74,

116.10, 73.30, 70.70, 69.02, 56.56 ppm; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33; Found: C, 68.90; H, 6.55; N, 6.99.

1-Acetamido-2-[(2-benzyloxy)ethoxy]ethane (27). A suspension of 1.2 g (28.99 mmol) of $LiAlH_4$ in 50 mL of anhydrous Et_2O was prepared in an oven dried three neck flask equipped with a gas inlet, a mechanical stirrer, a pressure equalizing addition funnel, a gas bubbler, and a condenser. A solution of **26** (5.46 g, 28.59 mmol) in 20 mL of anhydrous Et_2O was added dropwise, under Ar, at such a rate so as to keep the ether solution at reflux. Stirring was continued for 1 h after the addition was completed. After this time, the reaction was quenched by the careful successive addition of 1.2 mL of H_2O, 1.2 mL of 15% NaOH solution, and 3.6 mL of H_2O. Stirring was continued until a granular white precipitate formed. Filtration of the mixture yielded a clear, colorless ether filtrate, which was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield 5-benzyloxy-3-oxapentylamine, which was used without further purification to prepare **27**; IR (neat, cm^{-1}) 3350, 3290, 3050, 2920, 2890, 1610, 1460, 1360, 1100, 750, 700.

5-Benzyloxy-3-oxapentylamine was dissolved in 50 mL of Et_2O and treated with 5.79 g (57.2 mmol) of Et_3N and 3.65 g (35.7 mmol) of Ac_2O. The reaction mixture was stirred for 12 h at 27 °C, after which time the Et_2O was removed using a rotary evaporator. The resulting light brown syrup was dissolved in 250 mL of benzene and the organic phase was washed with saturated $NaHCO_3$ solution (2 x 100 mL), saturated brine (100 ml), dried (Na_2SO_4), filtered, and the filtrate concentrated *in vacuo* to give a light brown syrup. Kugelrohr distillation of the brown syrup yielded **27** (5.97 g, 88 % from **26**) as a clear, colorless syrup: bp 180 °C at 1 torr; IR (neat, cm^{-1}) 3296, 3080, 2950, 2880, 1720, 1653, 1553, 1460, 1283, 1190, 1135, 1100, 750, 700; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H, ArH), *6.41 (br s, 1 H, NH), 4.56 (s, 2 H, benzyl* CH_2), 3.64 (s, 4 H, OCH_2CH_2O), 3.51 (m, 4 H, OCH_2CH_2N), 1.90 (s, 3 H, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 170.22, 137.98, 128.45, 127.80, 73.30, 70.21, 69.83, 69.40, 39.28, 23.08 ppm; Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; Found: C, 65.65; H, 7.94; N, 5.84.

Methyl 3(5)-{[(2-Benzyloxy)ethoxy]methyl}pyrazole-5(3)-carboxylate (22). A mixture composed of **27** (3 g, 12.65 mmol) dissolved in 80 mL of a 1:1 mixture of CCl_4:glacial HOAc containing 6 g of anhydrous NaOAc was cooled to 3 °C in an ice/H_2O bath, treated with 5 mL of liquid N_2O_4, and then stirred for 1.5 h at 3 °C. Following this period, the solution was poured over 500 mL of ice/H_2O with subsequent vigorous stirring of the resultant mixture for 0.5 h. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (2 x 125 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to yield 1-*N*-nitrosoacetamido-2-[(2-benzyloxy)ethoxy]ethane (**28**) (3.36 g, 100%) as a light green syrup. This syrup showed no IR absorption at 3296 cm^{-1} (NH) or 1653 cm^{-1}(CO) to suggest unreacted **27.** *N*-Nitroso amide **28** made in this way was used immediately for subsequent reactions: IR (neat, cm^{-1}) 3080, 3040, 2882, 1735, 1505, 1485, 1250, 1115, 962, 948, 795, 745, 700.

N-Nitroso amide **28** (3.25 g, 12.23 mmol) was dissolved in 50 mL of Et_2O and mixed vigorously with an ice cold solution of 8.5 g of KOH dissolved in 15 mL of H_2O. The mixture was stirred at 3 °C for 45 min after which the IR spectrum of the ether layer showed the formation of a strong band at 2067 cm^{-1} (CHN_2) and no band at 1505 cm^{-1} (NO). The reaction mixture was then diluted with Et_2O (100 mL) and H_2O (200 mL) and the layers separated. The Et_2O layer was washed with H_2O (50 mL) and dried rapidly first

by swirling the ether phase over KOH pellets and decantation followed by anhydrous $MgSO_4$. Following filtration, the golden colored filtrate containing 1-diazo-2-[(2-benzyloxy)ethoxy]ethane (**23**) was used immediately in subsequent reactions: IR (neat, cm^{-1}) 3090, 3032, 2067, 1463, 1368, 1250, 1100, 750, 700.

The aforementioned filtrate containing **23** was added to a solution of 1.25 g (15 mmol) of methyl propiolate in 10 mL anhydrous Et_2O. The mixture was stirred at 27 °C for 4 h after which TLC analysis (hexane:EtOAc, 1:1) indicated that the reaction had proceeded to completion (during this time, the solution color changed from golden to light yellow). The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (EtOAc:hexane, 1:1) yielding **22** (2.16 g, 59% from **27**) as a colorless syrup: R_f =0.5 (EtOAc:hexane, 75:25); IR (neat, cm^{-1}) 3233, 3010, 2885, 1725, 1450, 1233, 1100, 750; ^1H NMR ($CDCl_3$) δ 12.98 (br s, 1 H, pyrazole NH), 7.28 (s, 5 H, ArH), 6.76 (s, 1 H, pyrazole H-4), 4.61 (s, 2 H, pyrazole-CH_2), 4.53 (s, 2 H, $ArCH_2O$), 3.86 (s, 3 H, CH_3), 3.63 (s, 4 H, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 161.78, 144.23, 140.44, 137.57, 128.14, 127.54, 107.18, 72.99, 69.42, 69.04, 64.32, 51.75 ppm; Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65; Found: C, 61.85; H, 6.10; N, 9.54.

3(5)-{[(2-Benzyloxy)ethoxy]methyl}pyrazole-5(3)-carboxamide (29). A solution of **22** (0.9 g, 3.1 mmol) in 15 mL of freshly distilled MeOH was saturated with NH_3 at 3 °C and the resulting mixture heated in a sealed glass tube at 115 °C for 40 h. Upon cooling, TLC analysis (EtOAc:hexane, 75:25) indicated that the reaction had proceeded to completion. The solution was then concentrated *in vacuo* and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH:H_2O, 65:10:4, lower phase) to yield **29** (0.8 g, 94%) as a white solid. Recrystallization of this material from EtOH/benzene afforded white crystals: mp 86-88 °C; R_f =0.43 ($CHCl_3$:MeOH:H_2O, 65:10:4, lower phase); IR (KBr, cm^{-1}) 3360, 3200, 3090, 2880, 2800, 1680, 1660, 1610, 1580, 1510, 1410, 1360, 1305, 1105, 766, 690; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 12.83 (br s, 1 H, pyrazole NH), 7.30 (s, 5 H, ArH), 6.73 (s, 1 H, pyrazole H-4), 4.49 (br s, 2 H, $CONH_2$), 4.60 (s, 2 H, pyrazole-CH_2), 4.52 (s, 2 H, $ArCH_2O$), 3.64 (s, 4 H, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 164.31, 145.62, 141.23, 138.03, 128.34, 127.74, 127.58, 105.37, 73.14, 69.51, 69.40, 64.14 ppm; Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26; Found: C, 61.31; H, 6.23; N, 15.05.

3(5)-[(2-Hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide (3). A solution of 500 mg (91.8 mmol) of **29** in 20 mL of a 3:1 mixture of EtOH:cyclohexene was treated with 100 mg of PdO•xH_2O. The mixture was refluxed for 1 h after which TLC analysis ($CHCl_3$:MeOH:H_2O, 65:10:4, lower phase) showed complete loss of starting material. The reaction mixture was cooled and filtered through a pad of celite that had been pre-washed with hot EtOH; the celite pad was then washed with hot EtOH, and the combined filtrates concentrated *in vacuo*. The resulting pale yellow syrup was purified by column chromatography using silica gel (MeCN:H_2O, 94:6) to yield **3** (310 mg, 95%) as a white solid. Recrystallization from EtOH/MeCN afforded **3** as white needles: mp 123-124 °C; R_f =0.5 (MeCN:H_2O, 94:6); IR (KBr, cm^{-1}) 3360, 3200, 3090, 2985, 2910, 2875, 1670, 1610, 1510, 1410, 1105, 765, 685; ^1H NMR (DMSO-d_6) δ 13.20 (br s, 1 H, D_2O exch, pyrazole NH), 7.52 (br d, 2 H, D_2O exch, NH_2), 6.57 (s, 1 H, pyrazole H-4), 4.51 (s, 2 H, pyrazole-CH_2), 3.47 (s, 1 H, D_2O exch, OH), 3.37 (m, 4 H, CH_2CH_2); ^{13}C NMR (DMSO-d_6) δ 163.55, 146.76, 141.12, 104.77, 71.46, 62.52, 60.03 ppm; Anal.

Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69; Found: C, 45.47; H, 6.12; N, 22.68.

3-Benzyloxy-1,1-dibromopropene (33). To an oven dried flask equipped with a mechanical stirrer, gas inlet, two pressure-equalizing addition funnels, and gas bubbler was added a mixture of dry/distilled CH_2Cl_2 (150 ml) and oxalyl chloride (35 mL of a 2.0 M solution in hexane (70 mmol oxalyl chloride)) under Ar. The addition funnels were charged with 10 mL (141 mmol) anhydrous DMSO in 30 mL CH_2Cl_2 and 9 g (59 mmol) 2-benzyloxyethanol (**31**)[10] in 60 mL dry/distilled CH_2Cl_2, respectively. The reaction flask was cooled to -78 °C and the DMSO solution added dropwise (<5 min), with stirring, to the oxalyl chloride solution. Upon completion of the addition, the alcohol solution was added dropwise to the reaction mixture, and the reaction mixture was allowed to stir at -78 °C for 10 min. After this period of time, anhydrous Et_3N (42 mL, 300 mmol) was added dropwise to the reaction mixture and the mixture was then allowed to warm to room temperature. Water (300 mL) was then added to the reaction mixture, the phases separated, and the aqueous phase extracted with CH_2Cl_2 (300 mL). The combined organic phases were washed with saturated NaCl solution (300 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow syrup gave a positive 2,4-dinitrophenylhydrazone test, indicating conversion to the aldehyde (**32**), which was used without further purification for the next reaction sequence.

The crude aldehyde **32** (assumed 59 mmol) was dissolved in dry/distilled CH_2Cl_2 (30 mL) and added dropwise, with mechanical stirring, at 0 °C, to a reagent prepared from the addition of 15 g (240 mmol) of Zn dust and 79.6 g (240 mmol) of CBr_4 to 79.6 g (240 mmol) triphenylphosphine in 300 mL of dry/distilled CH_2Cl_2 at 0 °C and allowing the reagent to warm to room temperature and stir for 12 h. The reaction mixture was allowed to stir at room temperature for 1.5 h after which 1200 mL of pentane was added. The reaction mixture was then filtered by suction filtration and the remaining residue re-extracted by dissolving it in CH_2Cl_2 (300 mL), reprecipitating the solution with pentane (1200 mL), cooling in an ice/H_2O bath and filtering. This extraction procedure was repeated for three additional cycles. The combined filtrates were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil which was purified by silica gel chromatography (hexane:EtOAc, 9:1) to yield 6.25 g of **33** (34% from 2-benzyloxyethanol): bp 105 °C at 1 torr ; R_f = 0.5 (hexane:EtOAc, 9:1); IR (neat, cm^{-1}) 3066, 2925, 2880, 1628, 1430, 1100, 750, 700; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H, ArH), 6.63 (t, 1 H, CH), 4.51 (s, 2 H, $ArCH_2$), 4.04 (d, 2 H, CH_2).

Methyl 4-Benzyloxy-2-butynoate (30). A solution composed of **33** (6.29 g, 20.43 mmol) dissolved in 100 mL of anhydrous THF in an oven dried flask was cooled to -78 °C under Ar atmosphere. *n*-Butyllithium (42 mmol, 26.18 mL of a 1.6 M solution in hexanes) was then added to the reaction mixture dropwise, with stirring, under Ar. The mixture was stirred for 1 h at -78 °C after which 3.16 mL (40.87 mmol) of methyl chloroformate was added in one portion. The mixture was allowed to warm to room temperature and was then poured over 100 mL of saturated NH_4Cl solution. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 200 mL). The combined organic phases were then washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield a brown syrup. The syrup was purified by silica gel chromatography (hexane:EtOAc, 9:1) to yield 3.0 g of **30** (72 %): R_f = 0.31 (hexane:EtOAc, 9:1); IR (neat, cm^{-1}) 3033, 2970, 2860, 2233, 1725, 1440, 1270, 1250, 1095, 1065, 750, 700; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H, ArH), 4.60 (s, 2 H, $ArCH_2$), 4.27 (s, 2 H, CH_2), 3.77 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.53, 136.79,

128.50, 128.12, 83.59, 78.01, 72.05, 56.72, 52.71; Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; Found: C, 70.44; H, 5.69.

Methyl 3(5)-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-(benzyloxy)-methylpyrazole-5(3)-carboxylate (34). A mixture composed of **19** (1 g, 2.1 mmol) dissolved in 20 mL of a 1:1 mixture of CCl_4:glacial HOAc containing 1 g of anhydrous NaOAc was cooled to 3 °C in an ice/H_2O bath, treated with 4 mL of liquid N_2O_4, and then stirred for 1.5 h at 3 °C. Following this period, the solution was poured over 100 mL of ice/H_2O with subsequent vigorous stirring of the resultant mixture for 0.5 h. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (25 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to yield 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-nitrosoacetamido-**D**-allitol (**16**) as a light green syrup. This syrup showed no IR absorption at 3311 cm^{-1} (NH) or 1653 cm^{-1}(CO) to suggest unreacted **19**. The *N*-nitroso amide was used immediately for subsequent reactions: IR (neat, cm^{-1}) 1730,1500.

The *N*-nitroso amide prepared above (assumed 2.1 mmol) was dissolved in 10 mL of Et_2O and mixed vigorously with an ice cold solution of 1.2 g of KOH dissolved in 3 mL of H_2O. The mixture was stirred at 3 °C for 45 min after which the IR spectrum of the ether layer showed the formation of a strong band at 2065 cm^{-1} (CHN_2) and no band at 1500 cm^{-1} (NO). The reaction mixture was then diluted with Et_2O (20 mL) and H_2O (25 mL) and the layers separated. The Et_2O layer was washed with H_2O (10 mL) and dried rapidly first by swirling the ether phase over KOH pellets and decantation followed by anhydrous $MgSO_4$. Following filtration, the golden colored filtrate containing 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diazo-**D**-allitol (**10**) was used immediately in subsequent reactions: IR (neat, cm^{-1}) 2065.

The aforementioned solution of **10** was added to a solution of 0.64 g (3.15 mmol) of **30** in 10 mL anhydrous Et_2O. The mixture was stirred at 27 °C for 24 h after which TLC analysis (EtOAc:hexane, 1:1) indicated that the reaction had proceeded to completion (during this time, the solution color changed from golden to light yellow). The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (EtOAc:hexane, 1:1) yielding **34** (0.82 g, 60% from **19**) as a colorless syrup: R_f = 0.40 (EtOAc:hexane, 1:1); IR (neat, cm^{-1}) 3250, 3033, 2900, 1725, 1450, 1133, 1080, 750, 700; ^1H NMR ($CDCl_3$) δ 12.1 (br s, 1 H, pyrazole NH), 7.33 (m, 20 H, ArH), 5.5 (s, 1 H, H-1'), 4.9-3.58 (m, 15 H), 3.9 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 163.10, 143.58, 141.25, 138.00, 137.90, 137.48, 136.65, 128.67, 128.43, 128.34, 128.30, 128.25, 128.14, 127.87, 127.75, 127.73, 127.71, 127.65, 116.51, 81.13, 79.28, 76.93, 76.11, 73.42, 72.66, 72.51, 71.72, 67.42, 62.45, 51.75; Anal. Calcd for $C_{39}H_{40}N_2O_7$: C, 72.20; H, 6.22; N, 4.32; Found: C, 72.41; H, 6.20; N, 4.20.

3(5)-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-(benzyloxy)methyl-pyrazole-5(3)-carboxamide (35). A solution of **34** (830 mg, 1.28 mmol) in 20 mL of freshly distilled MeOH was saturated with NH_3 at 3 °C and the resulting mixture heated in a sealed glass tube at 115 °C for 16 h. Upon cooling, TLC analysis (EtOAc:hexane, 6:4) indicated that the reaction had proceeded to completion. The solution was then concentrated *in vacuo* and the residue purified by column chromatography (EtOAc:hexane, 6:4) yielding **35** (790 mg, 97%) as a colorless syrup: R_f = 0.42 (EtOAc:hexane, 6:4); IR (neat, cm^{-1}) 3300, 3200, 3020, 2910, 2800, 1690, 1590, 1450, 1380, 1200, 1100, 1080,

750, 700; ^{1}H NMR ($CDCl_3$) δ 12.5 (br s, 1 H, pyrazole NH), 7.25 (m, 20 H, ArH), 6.30 (br d, 2 H, NH_2), 5.47 (s, 1 H, H-1'), 4.9-3.58 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 164.58, 143.78, 142.75, 137.93, 137.77, 137.44, 136.68, 128.56, 128.23, 128.01, 127.69, 114.90, 80.72, 79.37, 76.00, 73.51, 72.38, 72.27, 71.56, 68.15, 62.52; Anal. Calcd for $C_{38}H_{39}N_3O_6$: C, 72.02; H, 6.20; N, 6.63; Found: C, 72.17; H, 6.10; N, 6.43.

4-(Hydroxymethyl)-3(5)-(β-D-ribofuranosyl)pyrazole-5(3)-carboxamide (Homopyrazofurin) (4). A solution of **35** (748 mg, 1.18 mmol) in 20 mL of a 3:1 mixture of EtOH:cyclohexene was treated with 100 mg of palladium(II) oxide hydrate. The mixture was refluxed for 2 h after which TLC analysis (EtOAc:*n*-PrOH:H_2O, 4:1:2 (upper phase)) showed complete loss of starting material. The reaction mixture was then cooled, filtered through a pad of celite that had been washed with hot EtOH, the celite pad was then washed with hot EtOH, and the combined filtrates concentrated. The resulting colorless glass was purified by column chromatography using silica gel (EtOAc:EtOH:H_2O, 6:2:1) to yield **4** (226 mg, 70%) as a colorless glass; R_f = 0.25 (EtOAc:*n*-PrOH:H_2O, 4:1:2 (upper phase)); IR (neat, cm^{-1}) 3500-3100, 2900, 1680, 1600; ^{1}H NMR (DMSO-d_6) δ 7.59 (br d, 2 H, NH_2), 5.31 (br s, D_2O exch., 2 H), 5.29 (br s, D_2O exch., 1 H), 4.78 (d, 1 H, *J*= 5.8 Hz), 4.52 (s, 2 H, CH_2), 3.94-3.32 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 164.81, 143.08, 140.70, 119.52, 84.95, 75.85, 75.53, 70.70, 61.44, 52.88 ppm; Anal. Calcd for $C_{10}H_{15}N_3O_6$• 0.5 CH_3OH: C, 43.60; H, 5.92; N, 14.53; Found: C, 43.73; H, 5.76; N, 14.52.

Methyl 3(5)-{[(2-benzyloxy)ethoxy]methyl}-4-(benzyloxy)methyl-pyrazole-5(3)-carboxylate (36). A mixture composed of **27** (1.16 g, 4.9 mmol) dissolved in 30 mL of a 1:1 mixture of CCl_4:glacial HOAc and 2.32 g of anhydrous NaOAc was cooled to 3 °C in an ice/H_2O bath, treated with 2 mL of liquid N_2O_4, and stirred for 1.5 h at 3 °C. Following this period, the solution was poured over 200 mL of ice/H_2O with subsequent vigorous stirring of the resultant mixture for 0.5 h. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo* to yield **28** as a light green syrup. This syrup showed no IR absorption at 3296 cm^{-1} (NH) or 1653 cm^{-1}(CO) to suggest unreacted **27**. The *N*-nitrosoamide prepared in this manner was used immediately for the next reaction.

A solution composed of **28** prepared above (assumed 4.9 mmol) dissolved in 12 mL of Et_2O was mixed vigorously with an ice cold solution of 3.3 g of KOH dissolved in 6 mL of H_2O. The mixture was stirred at 3 °C for 45 min after which the IR spectrum of the Et_2O layer showed the formation of a strong band at 2067 cm^{-1} (CHN_2) and no band at 1505 cm^{-1} (NO). The reaction mixture was then diluted with Et_2O (50 mL) and H_2O (50 mL) and the layers separated. The Et_2O layer was washed with H_2O (50 mL) and dried rapidly first by swirling the ether phase over KOH pellets and decantation followed by treatment with anhydrous $MgSO_4$ and filtration. The golden colored filtrate containing **23** was used immediately in the subsequent reaction.

The aforedescribed solution of **23** (assumed 4.9 mmol) was added to a solution of **30** (0.5 g, 2.45 mmol) in 10 mL Et_2O and the reaction mixture stirred at 25 °C for 18 h. The Et_2O solution was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow syrup. This syrup was purified by silica gel chromatography (EtOAc:hexane, 75:25) to yield 0.5 g (50%) of **36** as a colorless syrup: R_f = 0.38 (EtOAc:hexane, 75:25);

IR (neat, cm^{-1}) 3220, 3033, 2880, 1725, 1460, 1375, 1150, 1100, 750, 700; ^1H NMR ($CDCl_3$) δ 7.30 (s, 10 H, ArH), 4.78 (s, 2 H, CH_2), 4.70 (s, 2 H, CH_2), 4.57 (s, 2 H, CH_2), 4.54 (s, 2 H, CH_2), 3.89 (s, 3 H, CH_3), 3.64 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 162.31, 143.62, 138.74, 138.25, 137.71, 128.39, 127.80, 127.64, 118.26, 73.30, 72.59, 70.05, 69.24, 64.20, 62.08, 51.90 ppm; Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39; N, 6.83; Found: C, 67.35; H, 6.47; N, 6.72.

3(5)-{[(2-Benzyloxy)ethoxy]methyl}-4-(benzyloxy)methylpyrazole-5(3)-carboxamide (37). A solution composed of 0.5 g of **36** (1.22 mmol) in 20 mL of anhydrous MeOH was cooled to 3 °C and saturated with anhydrous NH_3. The mixture was then heated in a sealed glass tube at 125 °C for 18 h. After this period of time the reaction was cooled and concentrated *in vacuo* to yield **37** as a colorless glass (0.475 g, 99%). This glass was crystallized from benzene/hexane to yield crystalline **37**: mp 84-85 °C (benzene/hexane); IR (KBr, cm^{-1}) 3300, 3200, 3100, 2880, 1680, 1600, 1100, 750, 700; ^1H NMR ($CDCl_3$) δ 7.27 (m, 12 H, ArH, NH_2), 4.80 (s, 2 H, CH_2), 4.63 (s, 2 H, CH_2), 4.50 (s, 4 H, 2 x CH_2), 3.59 (m, 4 H, CH_2CH_2); ^{13}C NMR ($CDCl_3$) δ 163.61, 144.75, 140.20, 137.87, 137.66, 128.39, 127.91, 127.74, 116.15, 73.19, 72.10, 69.56, 69.29, 64.25, 62.08 ppm; Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63; Found: C, 67.00; H, 6.41; N, 10.66.

3(5)-[(2-Hydroxyethoxy)methyl]-4-(hydroxymethyl)pyrazole-5(3)-carboxamide (5). Amide **37** (0.55 g, 1.39 mmol) was dissolved in 15 mL of absolute EtOH and the mixture treated with 5 mL of cyclohexene and 0.05 g $Pd(II)O{\cdot}xH_2O$. The mixture was refluxed for 1 h, cooled to room temperature, filtered through a pad of celite, the celite pad washed with hot EtOH and the combined filtrates concentrated *in vacuo* to yield a colorless glass. The colorless glass was crystallized from benzene/EtOH/hexane to yield 250 mg (84%) of **5**: mp 158-159 °C (benzene/EtOH/hexane); R_f = 0.55 ($CHCl_3$:MeOH, 7:3); ^1H NMR (DMSO-d_6) δ 7.62 (br d, 2 H, NH_2), 4.54 (s, 4 H, 2 x CH_2), 4.0 (br s, D_2O exch., 2 H, OH, OH), 3.47 (m, 4 H, CH_2CH_2); ^{13}C NMR (DMSO-d_6) δ 164.42, 142.05, 140.31, 120.05, 71.40, 61.92, 60.02, 53.09 ppm; Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53; Found: C, 44.65; H, 6.12; N, 19.44.

Dibenzyl Acetal of Bromoacetaldehyde (43).[34] To 17.2 g (0.02 mol) of freshly distilled vinyl acetate was added, with stirring, 32 g (0.2 mol) of Br_2 over a period of 2 h. The temperature was not allowed to go above 5 °C. To the resulting mixture was added, with stirring, 108 g (1 mol) of anhydrous benzyl alcohol over a period of 3 h. The reaction mixture was then allowed to come to room temperature slowly and then stirred overnight. After this time, 20 mL of H_2O was added to the vigorously stirred mixture, followed by small portions of K_2CO_3 until the solution was no longer acidic. The aqueous layer was removed *in vacuo* and the product remaining dried over anhydrous K_2CO_3. The fraction that distilled at 190-195 °C (2 mm)[34] was determined by ^1H NMR to be **43** (45 g, 70%); ^1H NMR ($CDCl_3$) δ 7.3 (s, 10 H, ArH), 4.9 (m, 1 H, CHO), 4.6 (d, J=4.6 Hz, 4 H, 2 x CH_2O), 3.4 (2, J=9.7 Hz, 2 H, CH_2Br); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.8, 128.4, 128.2 (phenyl), 100.8 (OCH), 68.8 (OCH_2), 31.9 (CH_2Br).

(Z)- and (E)-1-Benzyloxy-2-bromoethene (44 and 45, respectively). Freshly distilled diisopropylamine (2.64 g, 26 mmol) in 10 mL of distilled, dry THF was placed in a three-necked flask equipped with a cooling bath, mechanical stirrer, septum, gas inlet, and bubbler. The bath was then cooled to -61 °C ($CHCl_3/CO_2$) and 13.75 mL (22 mmol) of n-butyllithium in hexanes was added to the diisopropylamine solution through the septum. The resulting solution was stirred for 5-10 min and to this was added, under N_2

and dropwise, 3.21 g (10 mmol) of **43** by means of a pressure equalizing addition funnel. After the addition was complete, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. After this period, the mixture was poured into 50 mL of saturated aqueous NH_4Cl. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$) and filtered and the filtrate concentrated *in vacuo* to yield a dark brown syrup, which was purified by silica gel column chromatography (hexane) to the (E)-isomer **45** (R_f = 0.22, 0.43 g, 20%) and the (Z)-isomer **44** (R_f=0.08, 0.17 g, 8%).

^1H NMR for **45** ($CDCl_3$) δ 7.35 (s, 5 H, ArH), 6.84 (d, *J*=11.96 Hz, 1 H, OCH), 5.49 (d, *J*=11.96 Hz, 1 H, CHBr), 4.77 (s, 2 H, CH_2); ^{13}C NMR for **45** ($CDCl_3$) δ 148.89 (OCH), 127.43, 127.16, 127.00, 126.41 (phenyl), 82.68 (CHBr), 70.66 (CH_2).

^1H NMR for **44** ($CDCl_3$) δ 7.35 (s, 5 H, ArH), 6.64 (d, *J*=4.39 Hz, 1 H, OCH), 5.15 (d, *J*=4.39 Hz, 1 H, CHBr), 4.96 (s, 2 H, CH_2).

Benzyloxyacetylene (38). To a stirred slurry of sodamide prepared from freshly cut Na (0.64 g, 28 mg-atom), liquid NH_3 (30 mL) and ferric nitrate (2-5 mg), 2.98 g (14 mmol) of **45** in 10 mL of anhydrous Et_2O was added dropwise at -42 °C ($MeCN/CO_2$). The stirring was continued for 1 h. After this period, the NH_3 was allowed to evaporate completely under N_2. The flask was then cooled to -23 °C (CCl_4/CO_2) and 3.5 mL of well cooled (-23 °C) saturated aqueous NaCl solution and anhydrous Et_2O (2 x 30 mL at -23 °C) were added. This mixture was shaken well. The ether phase was separated, dried ($MgSO_4$) and filtered and the filtrate evaporated *in vacuo* to yield 1.92 (103%) of **38** that was sufficiently pure for further reactions; IR (neat, cm^{-1}) 3319, 2157; ^1H NMR ($CDCl_3$) δ 7.4 (s, 5 H, ArH), 5.0 (s, 2 H, CH_2O), 1.56 (s, 1 H, alkyne CH); ^{13}H NMR ($CDCl_3$) δ 138, 129, 128.5, 127 (phenyl), 125 (OC of alkyne), 44 (CH_2O), 32 (terminal alkyne C).

2,3,5-Tri-*O*-benzyl-D-ribose (53). A solution of 10 g (67 mmol) of **D**-ribose in 200 mL of dry and distilled MeOH was cooled to 0 °C in an ice/H_2O bath and 1 mL of conc. H_2SO_4 was added dropwise with stirring. Upon completion of the addition, the reaction mixture was stored for 16 h at 4 °C. The solution was then neutralized by passage through a bed of pre-washed Amberlite IRA-400 (OH) basic ion exchange resin, and the eluate concentrated *in vacuo* and then under greater reduced pressure to give a yellow syrup. A portion of the syrup was crystallized by dissolving in EtOAc, cooling, scratching the glass flask containing the solution and allowing it to stand for several days at 4 °C. The remaining syrup could then be crystallized by seeding to yield a total of 7.7 g (70%) of methyl **D**-ribofuranoside (mp 78-80 °C, lit.[35] 79-80 °C): ^1H NMR (DMSO-d_6) δ 5.40 (d, 1 H, H-1'), 4.15-4.9 (m, 5 H), 3.25 (s, 3 H, OCH_3). This product was used in the next step.

To a stirred solution of 4 g (24 mmol) of methyl **D**-ribofuranoside in 30 mL of dry and distilled THF was added 18 g (320 mmol) of finely powdered KOH. Benzyl chloride was added and the mixture heated, with stirring, under reflux for 24 h. Upon cooling, the reaction was filtered, the filtered solid was washed thoroughly with THF, and the combined filtrates concentrated *in vacuo* to yield a yellow syrup. The syrup was purified by silica gel column chromatography (toluene:EtOAc, 9:1) to yield 7.7 g (75%) of methyl 2,3,5-tri-*O*-benzyl-**D**-ribofuranoside[35] as a colorless syrup: R_f = 0.8 (toluene:EtOAc,

9:1); ^{1}H NMR (DMSO-d_6) δ 7.25 (m, 15 H, ArH), 4.90 (d, 1 H, H-1'), 3.4-4.6 (m, 11 H), 3.3 (s, 3 H, OCH_3).

To a solution of 4.46 g (10.4 mmol) of methyl 2,3,5-tri-*O*-benzyl-**D**-ribofuranoside dissolved in 100 mL of dioxane was added 25 mL of 0.1 *N* HCl and the resulting mixture heated to reflux temperature for 2 h. After this period of time, the reaction mixture was cooled to room temperature, neutralized with 1 *N* NaOH, and concentrated under reduced pressure. The remaining residue was dissolved in in 100 mL of $CHCl_3$ and this solution was washed with H_2O (3 x 100 mL), dried ($MgSO_4$) , filtered and the filtrate concentrated to give a yellow syrup. The syrup was purified by silica gel chromatography (toluene:EtOAc, 9:1) to yield 3.4 g (80%) of **53** as a light yellow syrup[35]: R_f = 0.2 (toluene:EtOAc, 9:1); ^{1}H NMR (DMSO-d_6) δ 7.25 (m, 15 H, ArH), 5.35 (d, 1 H, H-1'), 3.4-4.6 (m, 12 H).

Ethyl 4-Bromoacetoacetate (57a). Bromine (45.4 mL, 0.88 mol) was added dropwise to a solution of ethyl acetoacetate (102 g, 0.78 mol) in 200 mL of CS_2 at 0 °C. The solution was stirred for 2 days at room temperature. After cooling the solution, H_2O (300 mL) was added and the organic layer obtained by separation. The H_2O layer was extracted with Et_2O (300 mL) and the Et_2O layer combined with the organic layer obtained previously. The new organic mixture was dried ($MgSO_4$) and then concentrated under reduced pressure to give a crude product that was purified by distillation (97 °C/5 mm Hg) to yield 52 g (32%) of **57a**: ^{1}H NMR ($CDCl_3$) δ 4.15 (q, *J*=15 Hz, 2 H, $C\underline{H}_2CH_3$), 4.05 (s, 2 H, $C\underline{H}_2Br$), 3.63 (s, 2 H, $COC\underline{H}_2CO$), 1.22 (t, *J*=15 Hz, 3 H, $CH_2C\underline{H}_3$).

Ethyl 4-(Triphenylphosphonium)acetoacetate Bromide (57b). A solution of 41.8 g (0.2 mol) of **57a** in 200 mL of benzene was added dropwise to a stirred solution of 52.4 g (0.2 mol) of triphenylphosphine in 200 mL of benzene. An insoluble product appeared immediately but the mixture was allowed to set for 24 h. The material was isolated by filtration, washed with benzene and dried to yield **57b** (87.1%), mp 157-161 °C: R_f = 0.73 ($CHCl_3$:MeOH, 92:8); ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 15 H, ArH), 6.21 (d, 2 H, $Ph_3PC\underline{H}_2CO$), 4.05 (m, 4 H, $C\underline{H}_2CH_3$ and $COC\underline{H}_2CO$), 1.19 (t, 3 H, $CH_2C\underline{H}_3$).

3-Ethoxycarbonyl-2-oxopropylidenetriphenylphosphorane (56).[36] Compound **57b** (118 g) was added to a 10% aqueous solution of Na_2CO_3 and this mixture was stirred for 12 h. The resulting product was isolated by filtration, washed three times with H_2O, and dried for 24 h to give **56** (71.4 g, 70%) that was suitable for use in the next reaction with **53**. If desired, **56** could be purified by recrystallization from benzene to yield a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 16 H, ArH and =C$\underline{H}$), 4.22 (q, 2 H, $C\underline{H}_2CH_3$), 3.49 (s, 2 H, $COC\underline{H}_2CO$), 1.30 (t, 3 H, $CH_2C\underline{H}_3$).

Ethyl 3-Oxo-4-(2',3',5'-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)butanoate (54). By adapting a literature procedure[24] a solution of **53** (1.85 g, 4.4 mmol) and **56** (3.90 g, 10 mmol) in anhydrous MeCN (25 mL) was refluxed for 48 to 72 h. The MeCN was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography and the fraction eluting with hexane:EtOAc (5:1) contained a viscous oil of **54** (54-70%) as an α/β mixture (*ca.* 1:3) whose ^{1}H NMR spectrum was identical to that reported[24] for this mixture.

Ethyl 2-Diazo-3-oxo-4-(2',3',5'-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)butanoate (55). By adapting a literature procedure,[24] triethylamine (0.57 g, 5.6 mmol) and *p*-toluenesulfonyl azide (3.07 mL) were added to a solution of **54** (3.0 g, 5.6 mmol) in 25 mL of anhydrous MeCN. The mixture was kept at 15 °C overnight. After evaporation of the MeCN under reduced pressure, the residue was subjected to silica gel column chromatography and the fraction eluting with hexane-EtOAc (5:1) gave an α/β mixture of **55** (44%) as a viscous oil whose ^{1}H NMR spectrum was identical to that reported[24] for this mixture.

Ethyl 4-Hydroxy-3(5)-(2',3',5'-tri-*O*-benzyl-α- and -β-D-ribofuranosyl)pyrazole-5(3)-carboxylate (α-52 and β-52). By adapting a literature procedure,[24] a solution of 2.36 g (4.3 mmol) of **55** in 20 mL of dry THF was added dropwise to a stirred, ice-cooled suspension of 0.86 g (21 mmol, 60% dispersion) of sodium hydride in 20 mL of dry THF under N_2. A solution of 1.26 g (21 mmol) of HOAc in 10 mL of dry THF was then added dropwise to the stirred, ice-cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue to which were added 30 mL of H_2O and 30 mL of Et_2O. The Et_2O layer was separated, dried (Na_2SO_4) and concentrated and the residue subjected to silica gel column chromatography. The fraction eluting with hexane-EtOAc (3:1) yielded a mixture of α-**52** and β-**52** (1:3) as a foam (67%). The ^{1}H NMR spectrum of this mixture was identical to that reported[24] for this mixture.

4-Hydroxy-3(5)-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-(N-methyl)carboxamide (β-58). A solution of 460 mg (0.82 mmol) of **52** (α:β=1:3) in 10 mL of MeOH containing methylamine was heated at 100 °C for 12 h. The excess of methylamine was evaporated and the residue (490 mg) was subjected to silica gel column chromatography with hexane-EtOAc (3:1) to give β-**58** as a foam (250 mg, 54%); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 15 H, ArH), 5.43 (s, 1 H, H-1'), 4.45-4.85 (m, 6 H, 3 x benzyl CH_2), 3.5-4.3 (m, 5 H, H-2', H-3', H-4', and H-5'), 2.95 (d, 3 H, NCH_3).

Ethyl 1-Benzyl-4-benzyloxy-3(5)-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-carboxylate (61). A mixture of β-**52** (150 mg, 0.27 mmol), K_2CO_3 (100 mg, 0.72 mmol), benzyl bromide (150 mg, 0.88 mmol) and DMF (10 mL) was stirred for 12 h at room temperature. Water (50 mL) was added to this mixture, which was, in turn, extracted with Et_2O (3 x 50 mL). The combined ether extracts were washed with H_2O (3 x 50 mL) and the ether evaporated on rotary evaporator to give a residue that was subjected to silica gel column chromatography with hexane-EtOAc (3:1) to give **61** (180 mg, 91%) as a foam; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 25 H, ArH), 5.6 (s, 2 H, benzyl CH_2 at C-4 of pyrazole), 5.15 (d, 1 H, H-1'), 5.0 (s, 2 H, benzyl CH_2 on pyrazole ring nitrogen), 4.4-4.65 (m, 6 H, 3 x benzyl CH_2 on ribofuranosyl), 3.95-4.40 (m, 3 H, H-2', H-3', H-4'), 4.22 (q, 2 H, $C\underline{H}_2CH_3$), 3.53 (d, 2 H, H-5'), 1.2 (t, 3 H, $CH_2C\underline{H}_3$).

1-Benzyl-4-benzyloxy-3(5)-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-(N,N-dimethyl)carboxamide (62). A solution of **61** (500 mg, 0.68 mmol) in 20 mL of EtOH containing 10 mL of dimethylamine (prepared from a 25% aqueous solution of dimethylamine) was heated at 200 °C for 12 h. The excess dimethylamine was removed by evaporation and the residue was subjected to silica gel column chromatography with hexane-EtOAc (3:1) to give **62** as a foam (150 mg, 30%); ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 15 H, ArH), 5.35 (s, 2 H, benzyl CH_2 at C-4 of pyrazole), 5.17

(s, 1 H, H-1'), 3.3-4.7 (m, 13 H, H-2', H-3', H-4', H-5', 4 x benzyl CH_2 on ribofuranosyl), 2.74 (s, 6 H, 2 x CH_3).

1-Benzyl-4-benzyloxy-3(5)-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-5(3)-(N-cyclohexyl)carboxamide (63). A solution of **61** (180 mg, 0.24 mmol) in cyclohexylamine (5 mL) was heated at 100 °C for 20 h under pressure. The excess cyclohexylamine was removed by evaporation and the residue subjected to silica gel column chromatography using hexane-EtOAc (5:1) to give **63** (70 mg, 37%): mp 84-86 °C); ^{1}H NMR ($CDCl_3$) δ 7.15-7.35 (m, 25 H, ArH), 5.7 (s, 2 H, benzyl CH_2 at C-4 of pyrazole), 5.15 (d, 1 H, H-1'), 5.05 (s, 2 H, benzyl CH_2 on pyrazole ring nitrogen), 4.4-4.65 (m, 6 H, 3 x benzyl CH_2 on ribofuranosyl), 4.0-4.6 (m, 3 H, H-2', H-3', H-4'), 3.5 (d, 2 H, H-5'), 0.7-1.8 (m, 11 H, cyclohexyl H).

3,6-Anhydro-4,5,7-tri-O-benzyl-2-deoxy-β-D-*allo*- and β-D-*altro*-heptanoic Acid (Scheme 23). A solution of **66**[27] (1 g, 2.1 mmol) and 10 mL of 1*N* KOH (10 mL) in 10 mL of MeOH was refluxed for 1 h. To this mixture, 200 mL of $CHCl_3$ was added and the organic phase was separated and washed with 1*N* HCl. The $CHCl_3$ phase was dried ($MgSO_4$) and evaporated on a rotary evaporator to give 0.95 g (99%, α:β=1:5) of the heptanoic acid that was used directly for the next sequence of reactions. ^{1}H NMR for the heptanoic acid ($CDCl_3$) δ 7.9 (s, 1 H, OH), 7.25 (m, 15 H, ArH), 4.5 (m, 6 H, 3 x benzyl CH_2), 3.02-4.30 (m, 6 H, H-3, H-4, H-5, H-6, H-7), 2.79 (d, 2 H, side chain CH_2 of α-anomer), 2.55 (d, 2 H, side chain CH_2 of β-anomer).

Attempted Preparation of Ethyl 3-Hydroxy-4-(2',3',5'-tri-*O*-benzyl-β-D-ribofuranosyl)pyrrole-2-carboxylate (Precursor to 8 of Scheme 23). By adapting a literature procedure,[37] a solution of the heptanoic acid prepared above (1 g, 2.1 mmol) in 20 mL of Et_2O, thionyl chloride (20 mL), and DMF (2 drops) was heated at reflux for 3 h. The solvents were removed *in vacuo*, leaving a residue that was dissolved in and co-evaporated twice with dry benzene (30 mL). The resulting solid acid chloride was purified by silica gel column chromatography (hexane-EtOAc, 3:1) and the desired fraction isolated, dried at 35 °C (20 mm, 12 h), dissolved in dry benzene, and then used in the following reaction.

Triethylamine (0.22 g, 2.2 mmol) was added to the benzene solution of the acid chloride and this solution stirred for 2 h at room temperature. To this, a solution of methyl isocyanoacetate (Aldrich, 0.22 g, 2.2 mmol) and Et_3N (0.22 g, 2.2 mmol) was added with stirring. Following two days of stirring, TLC analysis indicated that starting material was consumed. Evaporation of the mixture produced a number of compounds that could not be adequately purified for identification.

Preparation of Enol Ester 67. A solution of **66**[27] (2 g, 4.2 mmol) and ethyl formate (0.47 g, 6.4 mmol) in Et_2O was added dropwise to a mixture of sodium hydride (0.14 g, 4.7 mmol, 80% in oil), Et_2O (20 mL) and EtOH (0.1 mL) at 0 °C. Stirring of this mixture was continued at room temperature overnight. After addition of EtOH (2 mL) to the mixture, H_2O (50 mL) was added and the resultant mixture was extracted with Et_2O (3 x 50 mL). Concentration of the dried ($MgSO_4$) Et_2O solution gave a residue that was subjected to adequate purification by silica gel column chromatography to yield a mixture (1.1 g, 55%) of the α,β/syn,anti isomers represented by **67**.

Preparation of Aminoacid Ester 68. A solution of **67** (500 mg, 0.1 mmol), ethyl glycinate (206 mg, 0.2 mmol) and Et_3N (50 mg) in benzene (100 mL) was refluxed for 2 days using a Dean-Stark trap. Concentration of the benzene solution using a rotary evaporator gave a residue, which was subjected to silica gel column chromatography (hexane-EtOAc) to give **68** (150 mg, 27%); ^1H NMR ($CDCl_3$) δ 7.25 (m, ArH), 4.25-4.80 (m, benzyl CH_2 and OCH_3), 4.15 (q, 2 H, $C\underline{H_2}CH_3$), 2.8-4.0 (m, ribofuranosyl ring H), 1.25 (t, 3 H, $CH_2C\underline{H_3}$).

Methyl α-Chloro-α-nitroacetate (69). A solution of 90% HNO_3 (82 mL) and 95% H_2SO_4 (100 mL) was added to 1,1,2-trichloroethene (198 g) at 10 °C over 1 h. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate added dropwise to MeOH (200 mL). This mixture was stirred overnight at room temperature and then heated to 50 °C. Upon cooling, the solution was concentrated on a rotary evaporator and the residue poured into ice (200 g). After the ice melted, the aqueous mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined $CHCl_3$ fractions were concentrated on a rotary evaporator and the residue distilled (65 °C/6 mm) to **69** (30 g, 30%); ^1H NMR ($CDCl_3$) δ 6.85 (s, 1 H, CH), 3.95 (s, 3 H, OCH_3).

1-*O*-Acetyl-(2',3',5'-tri-*O*-benzyl)-β-D-ribofuranose (76). A solution of **53** (20 g), Ac_2O (20 mL) and pyridine (20 mL) was stirred at room temperature overnight. Removal of unreacted Ac_2O and pyridine under vacuum gave a residue, which was clarified by silica gel column chromatography (hexane-EtOAc) to give **76** (17 g, 77%) that was used directly in the preparation of **73**. ^1H NMR for **76** ($CDCl_3$) δ 7.3 (m, 15 H, ArH), 6.2 (s, 1 H, H-1'), 3.5-4.7 (m, 11 H, H-2', H-3', H-4', H-5' and benzyl CH_2), 1.87 (s, 3 H, CH_3).

2,5-Anhydro-3,4,6-(tri-*O*-benzyl)-D-allonitrile (73). Compound **76** (16.6 g, 35.9 mmol) was dissolved in 100 mL of dry CH_2Cl_2 under N_2. The solution was treated with 6.3 mL (47.6 mmol) of trimethylsilyl cyanide[31] and 2.6 g (10 mmol) of anhydrous $SnCl_4$. The mixture was heated to reflux for 4 h under N_2. After cooling, the mixture was poured carefully over 200 g of ice. The resulting aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the organic extracts were combined, washed with 5% aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated on a rotary evaporator. The syrup which resulted was purified by silica gel column chromatography (using hexane-EtOAc, 3:1)to give **73** (5.3 g, 34%) and a derivative of **73** (3.8 g, 25%) lacking a benzyl substituent. ^1H NMR for **73** ($CDCl_3$) δ 7.3 (m, 15 H, ArH), 4.4-4.7 (m, 6 H, 3 x benzyl CH_2), 3.9-4.4 (m, 4 H, H-1', H-2', H-3', H-4'), 3.5 (d, 2 H, H-5').

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(33) For the purposes of obtaining the microanalytical data for **2,** methanol was used to transfer the sample to a small vial for delivery to M-H-W Laboratories and it was not possible to free the sample from all of the methanol to obtain an analysis free of this solvent.

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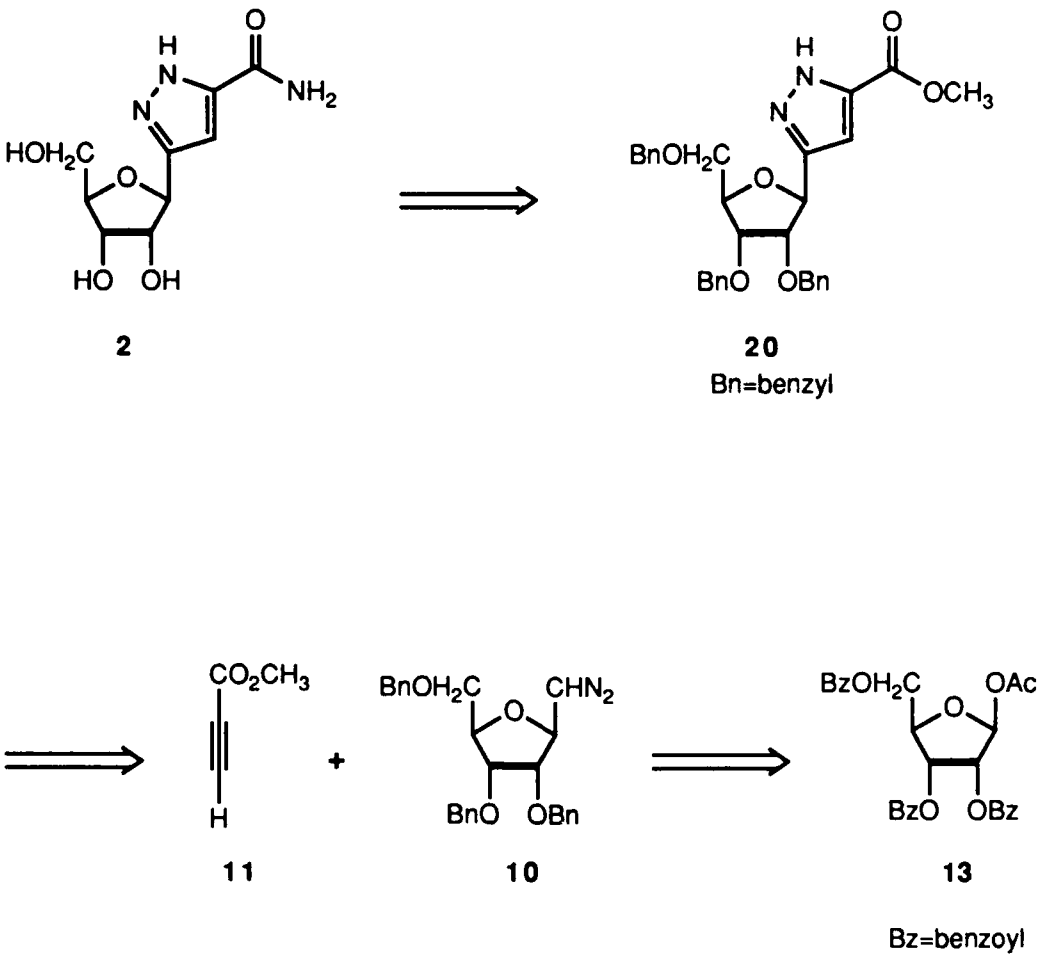
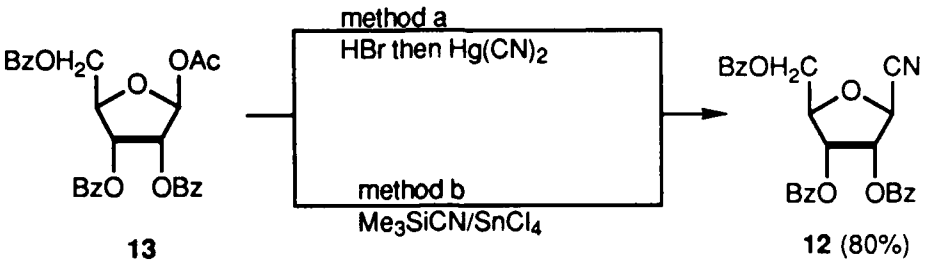
Scheme 1
Retrosynthetic Approach to 4-Deoxypyrazofurin



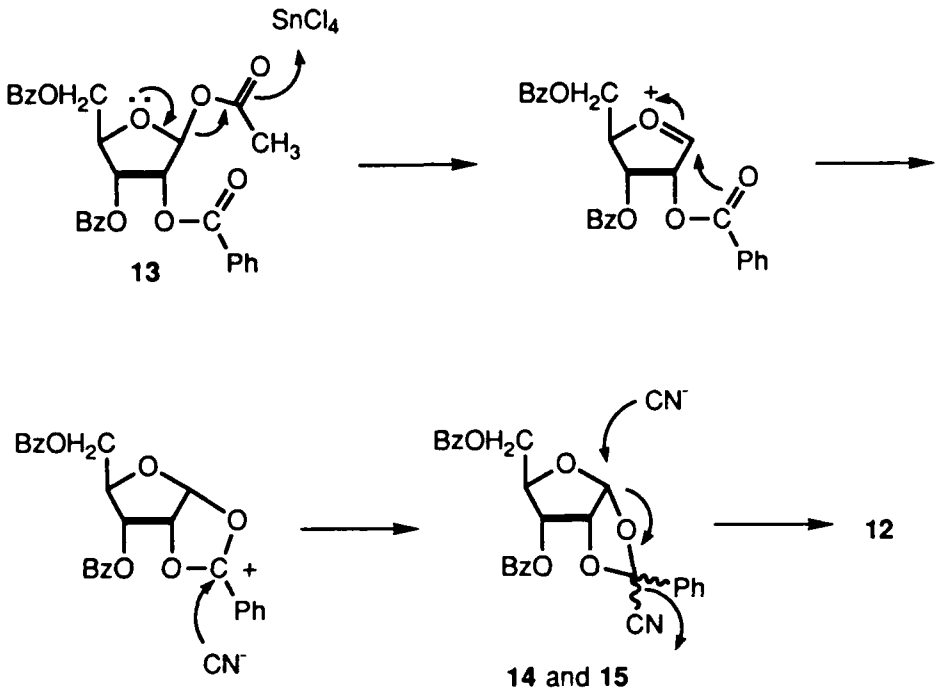
Scheme 2

The Preparation of 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-**D**-allonitrile (**12**)

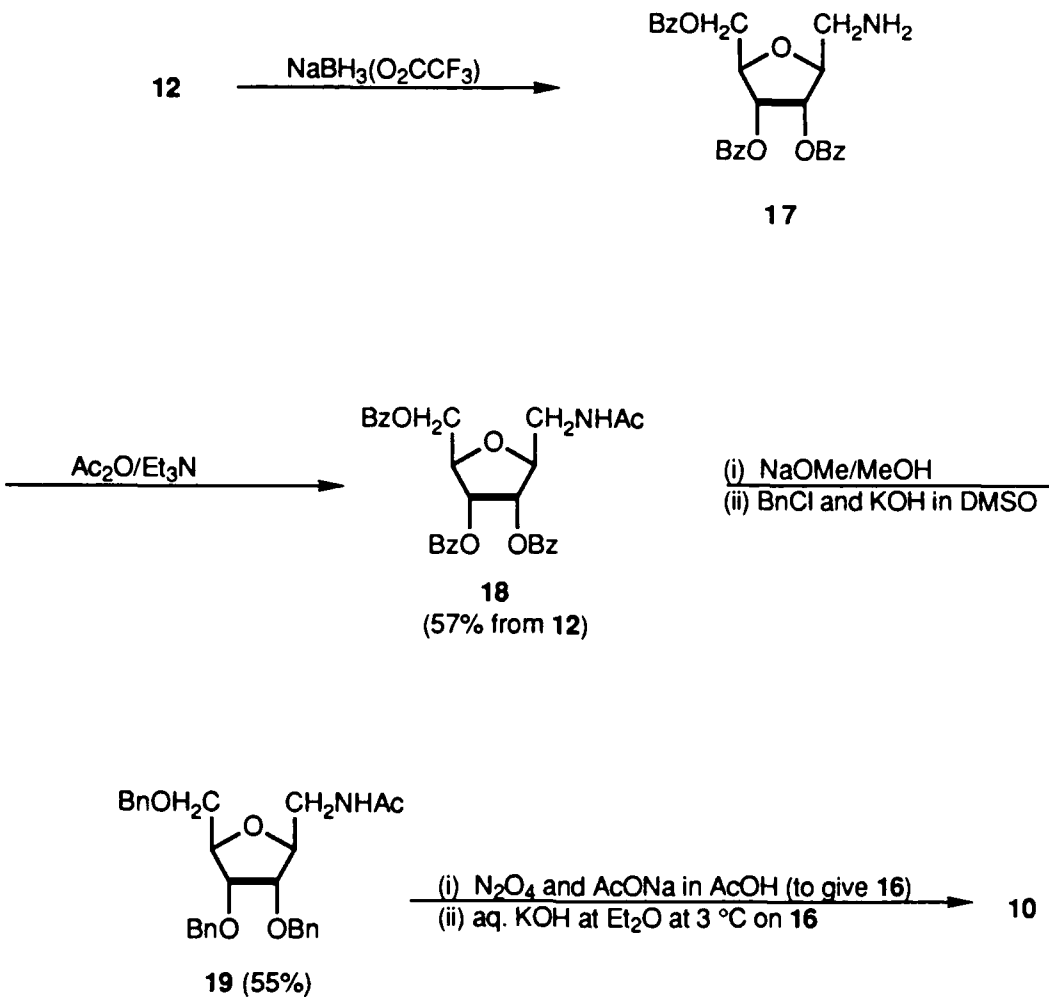


13 **12** (80%)

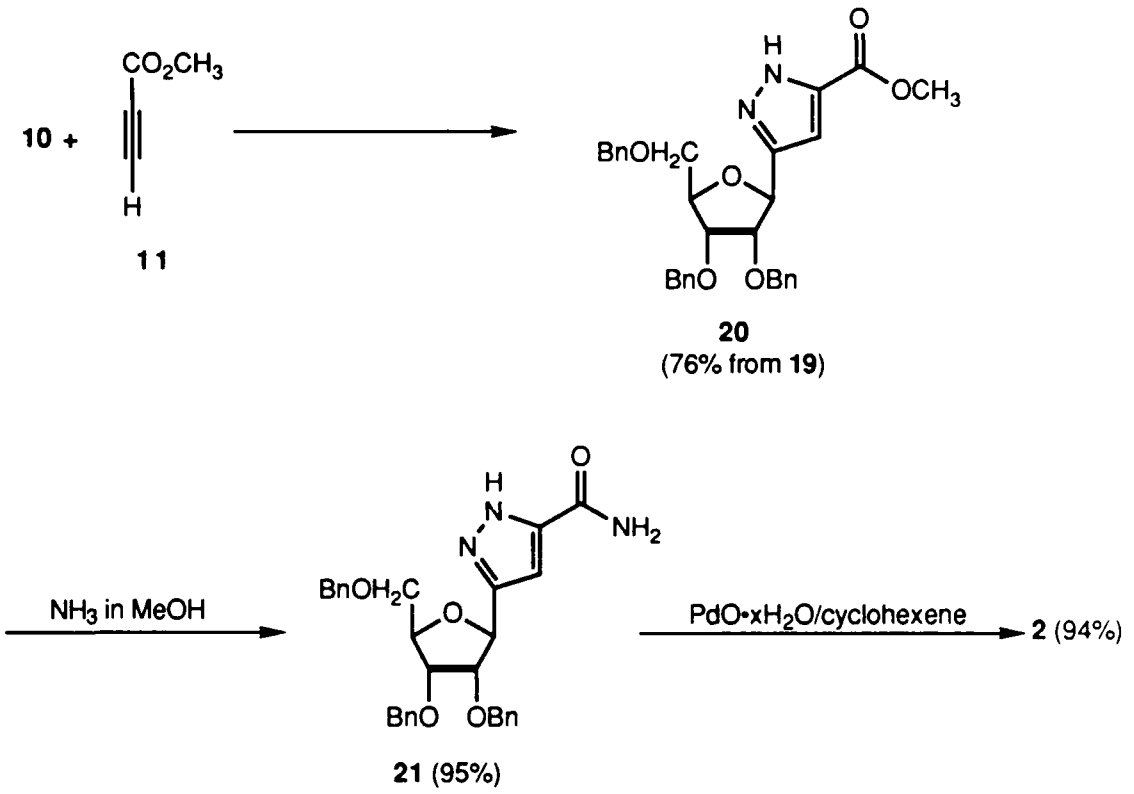
Scheme 3
Proposed Mechanism for the Stereospecific Formation of Nitrile **12**



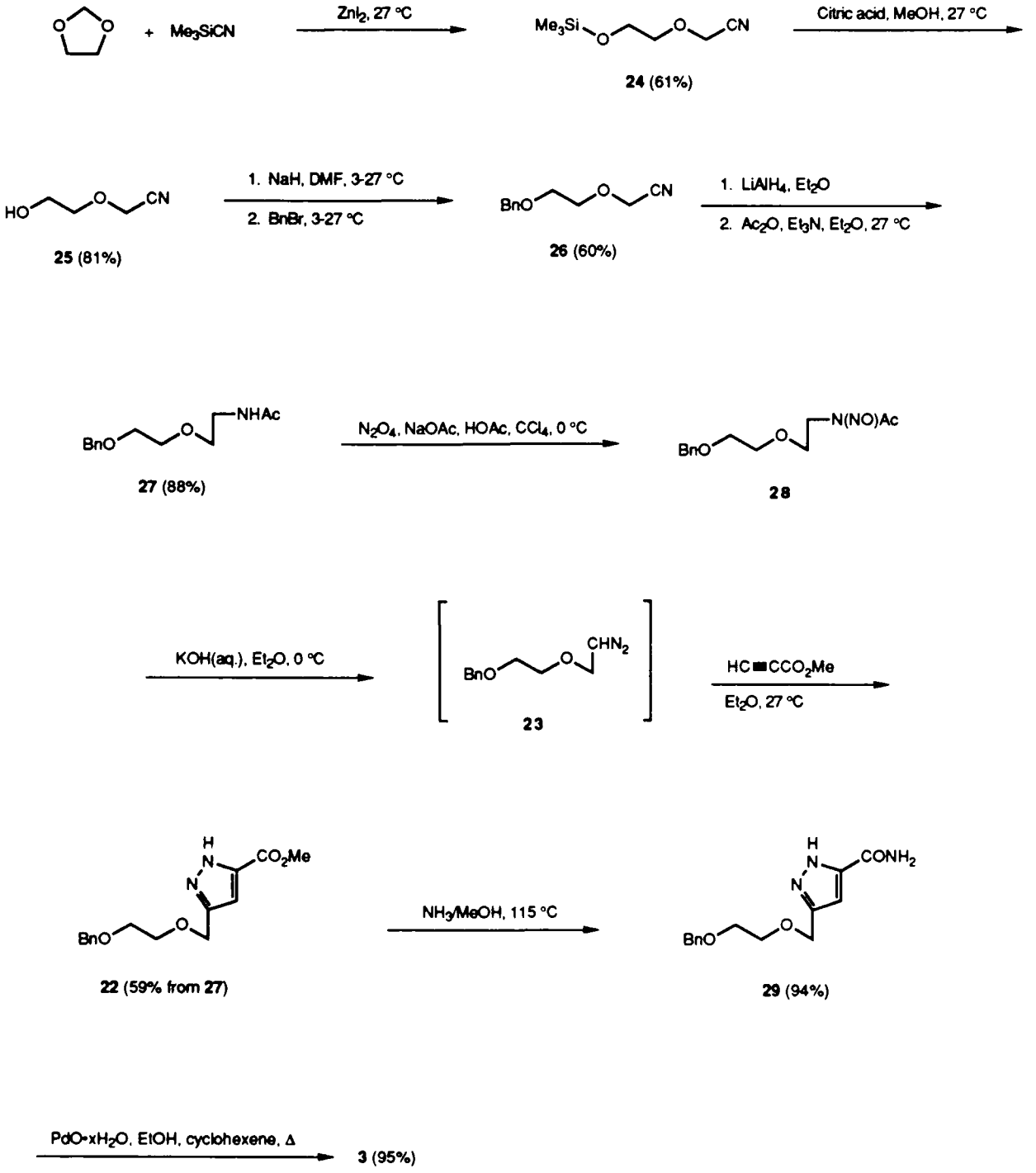
Scheme 4
Synthesis of Diazoribofuranose Derivative **10**



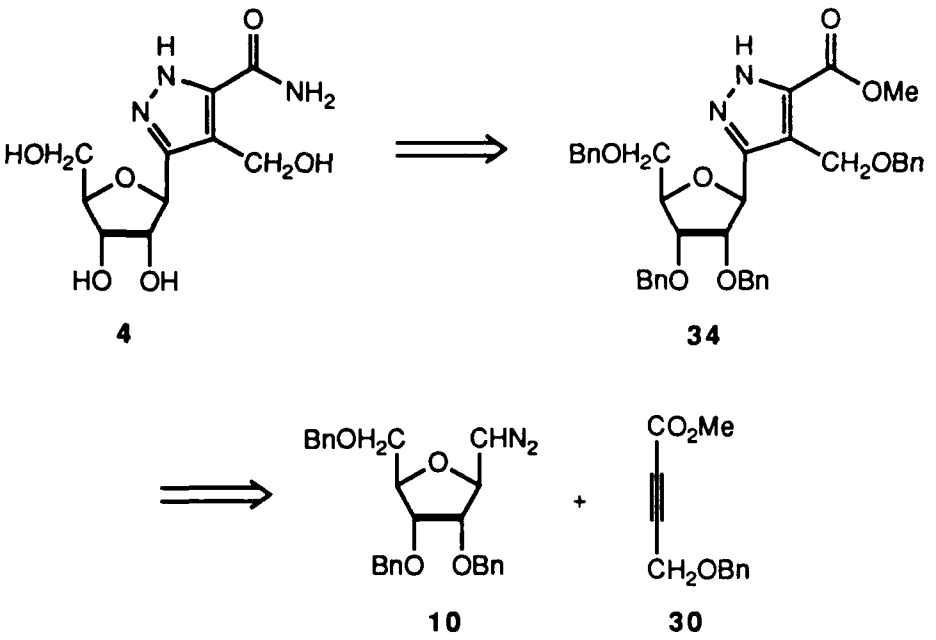
Scheme 5
Completion of the synthesis of 4-Deoxypyrazofurin (**2**)



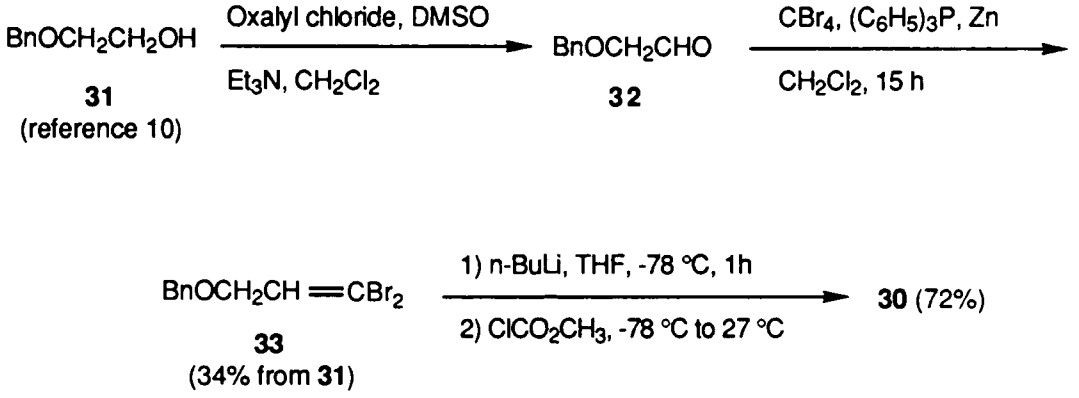
Scheme 6
Synthesis of Acyclo 4-Deoxypyrazofurin (**3**)



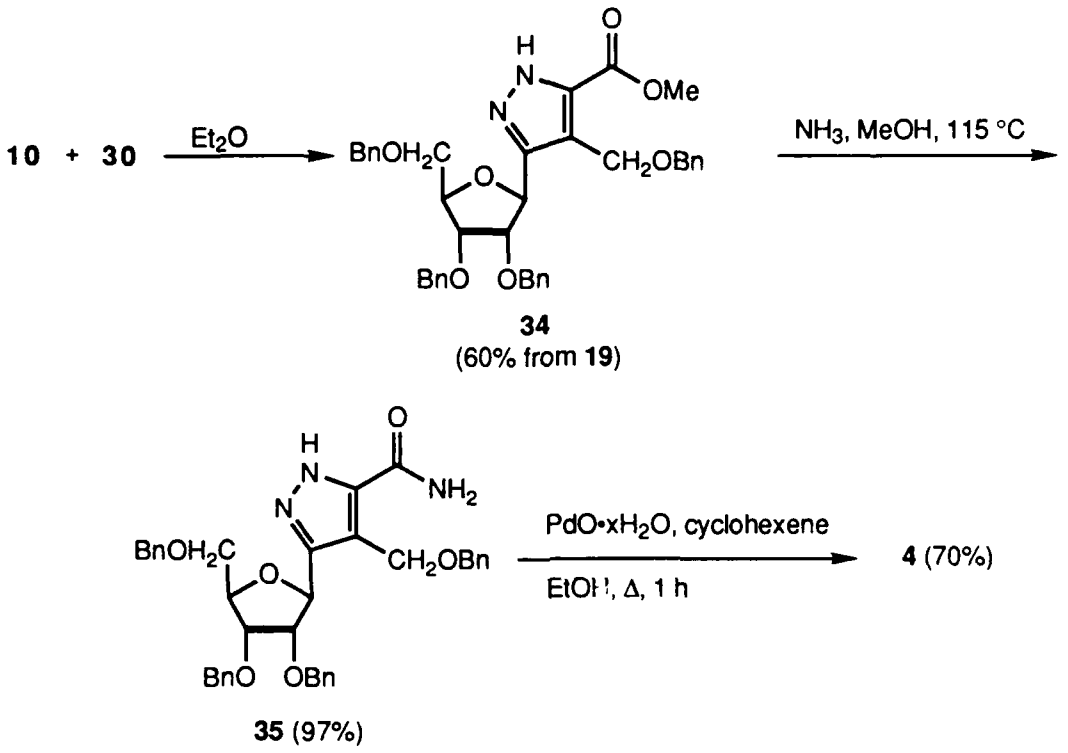
Scheme 7
Retrosynthetic Approach to 4-Homopyrazofurin (**4**)



Scheme 8
Synthesis of Methyl 4-Benzyloxy-2-butynoate (**30**)

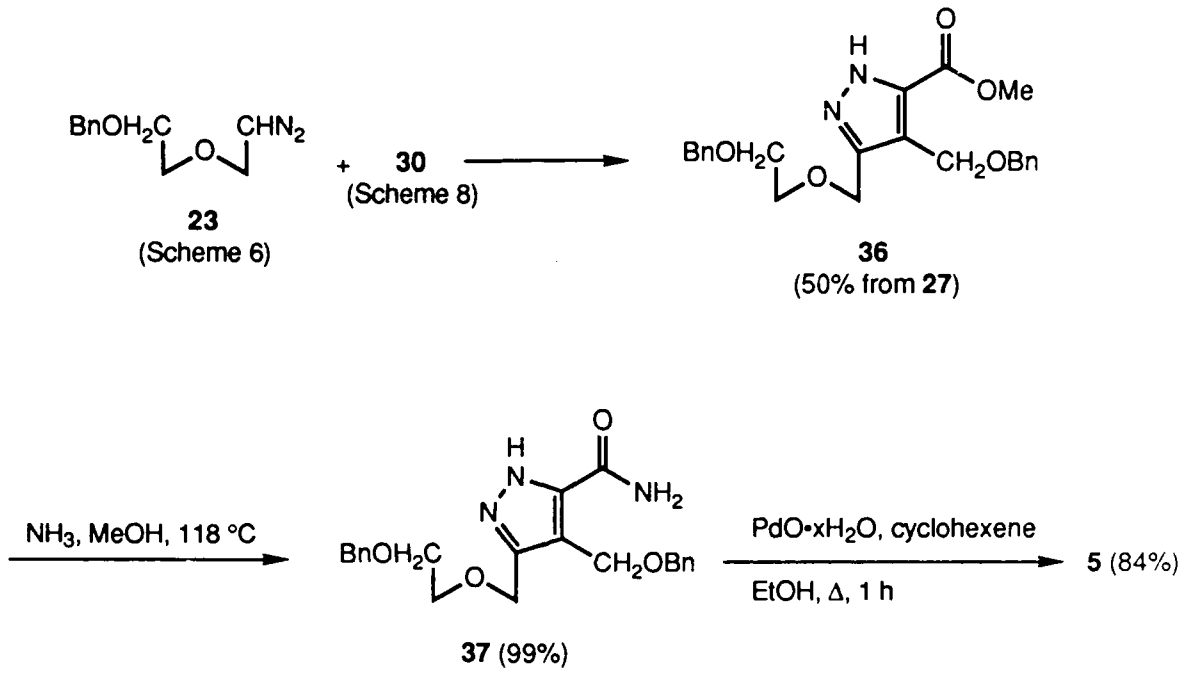


Scheme 9
Preparation of 4-Homopyrazofurin (**4**)

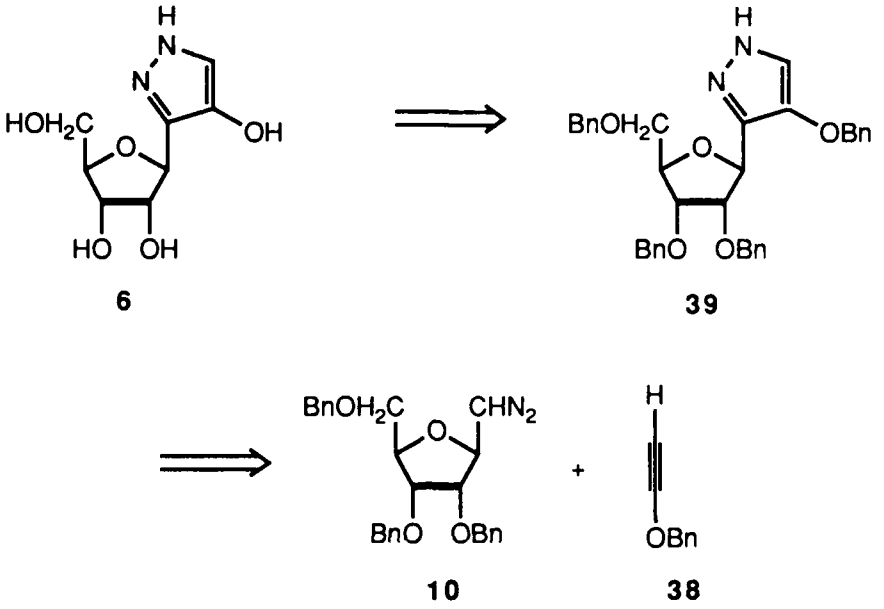


Scheme 10

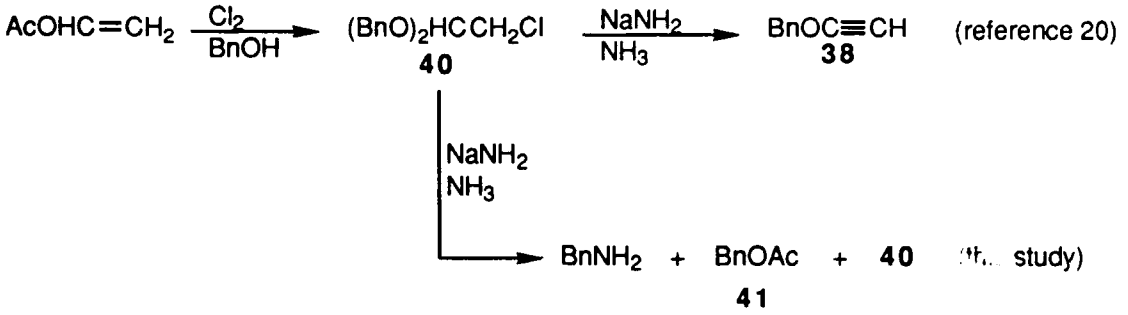
Preparation of the Acyclic Analogue of 4-Homopyrazofurin (**5**)



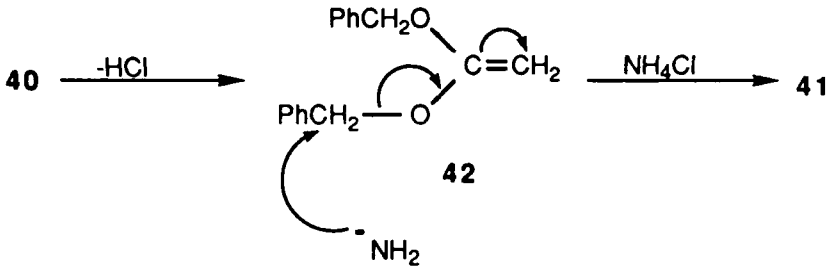
Scheme 11
Retrosynthetic Approach to Analogue (**6**)



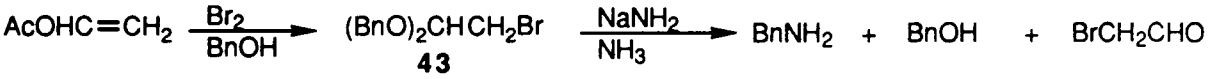
Scheme 12
Studies Related to the Synthesis of **38**



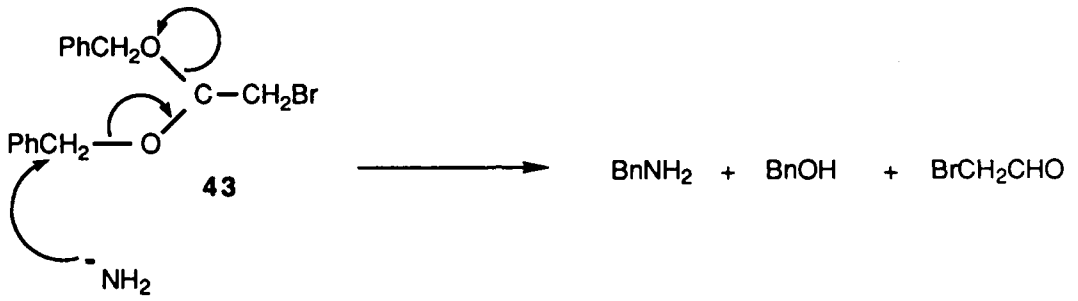
Possible mechanism for the formation of **41**:



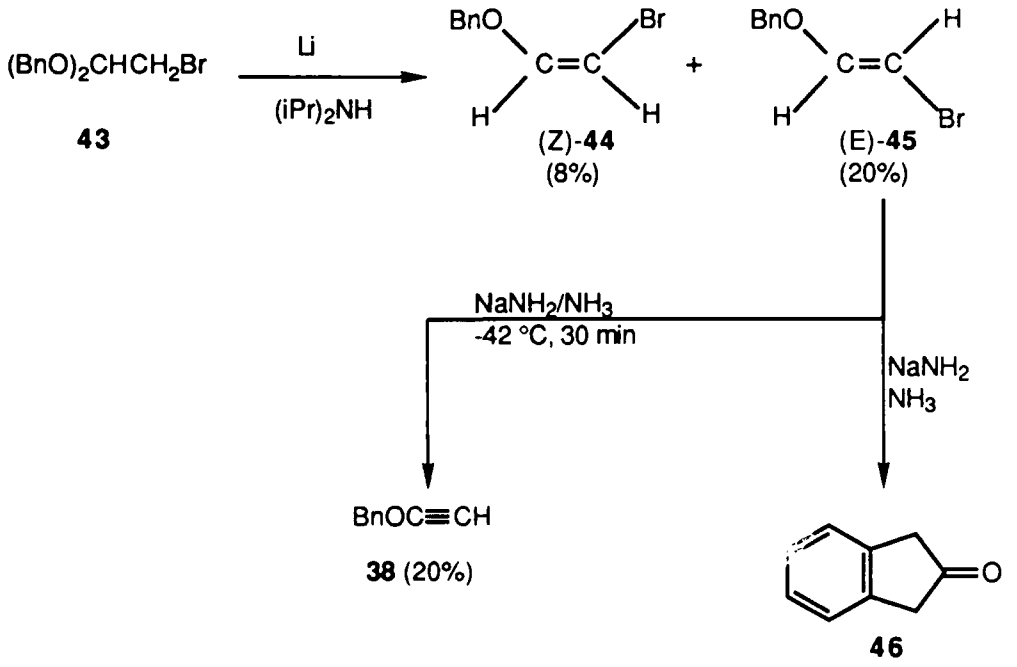
Scheme 13
Further Studies Related to the Synthesis of **38**



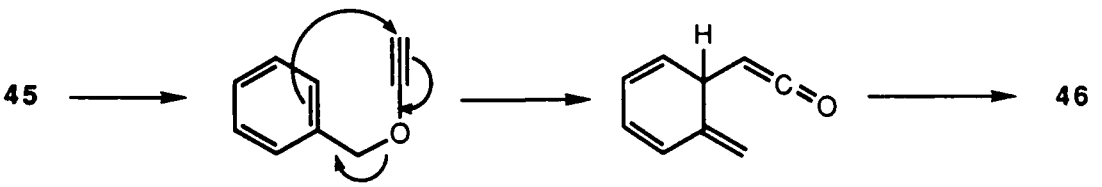
Possible mechanism for product formation:



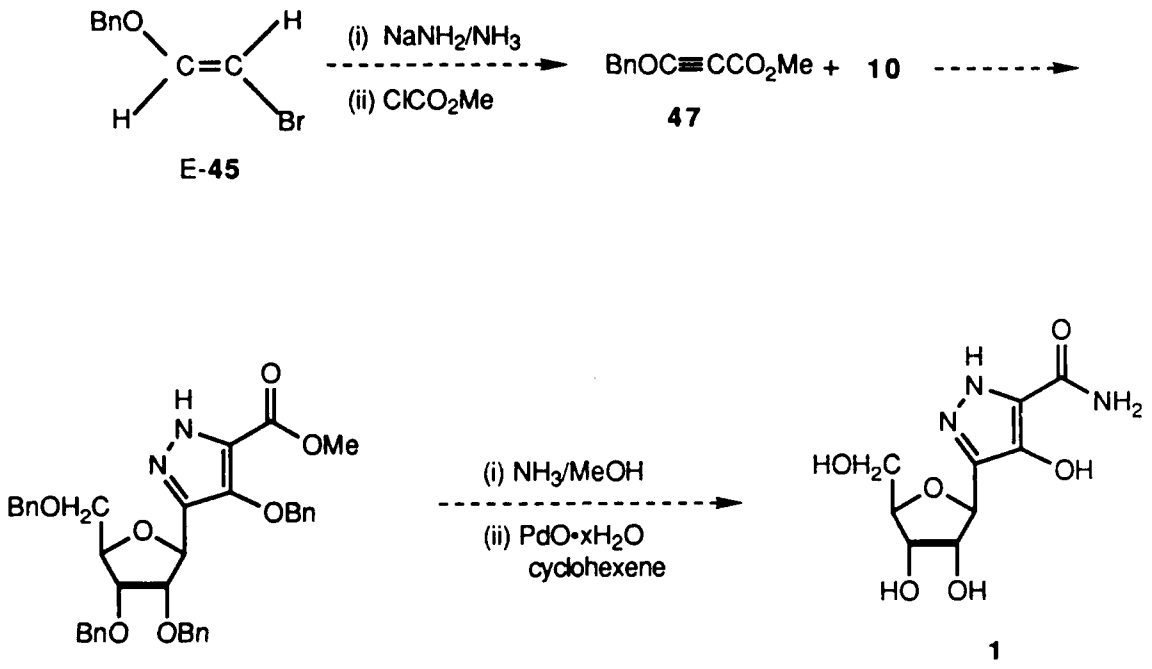
Scheme 14
Further Studies Related to the Synthesis of **38**



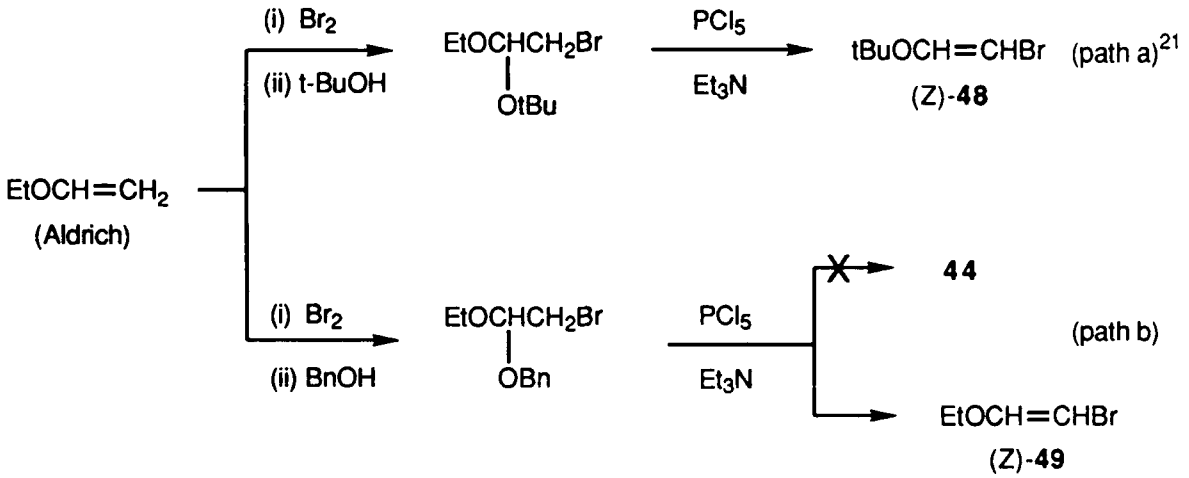
Possible mechanism for the formation of **46**:

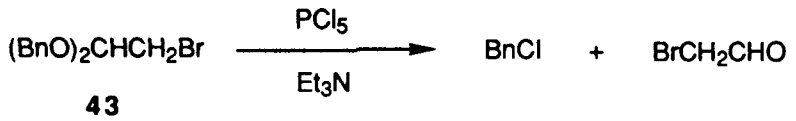


Scheme 15
Possible Route to Pyrazofurin (**1**)

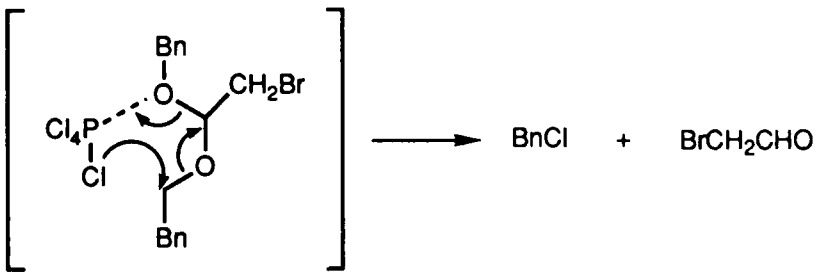


Scheme 16
Attempted Alternative Route to the (Z)-Isomer **45**

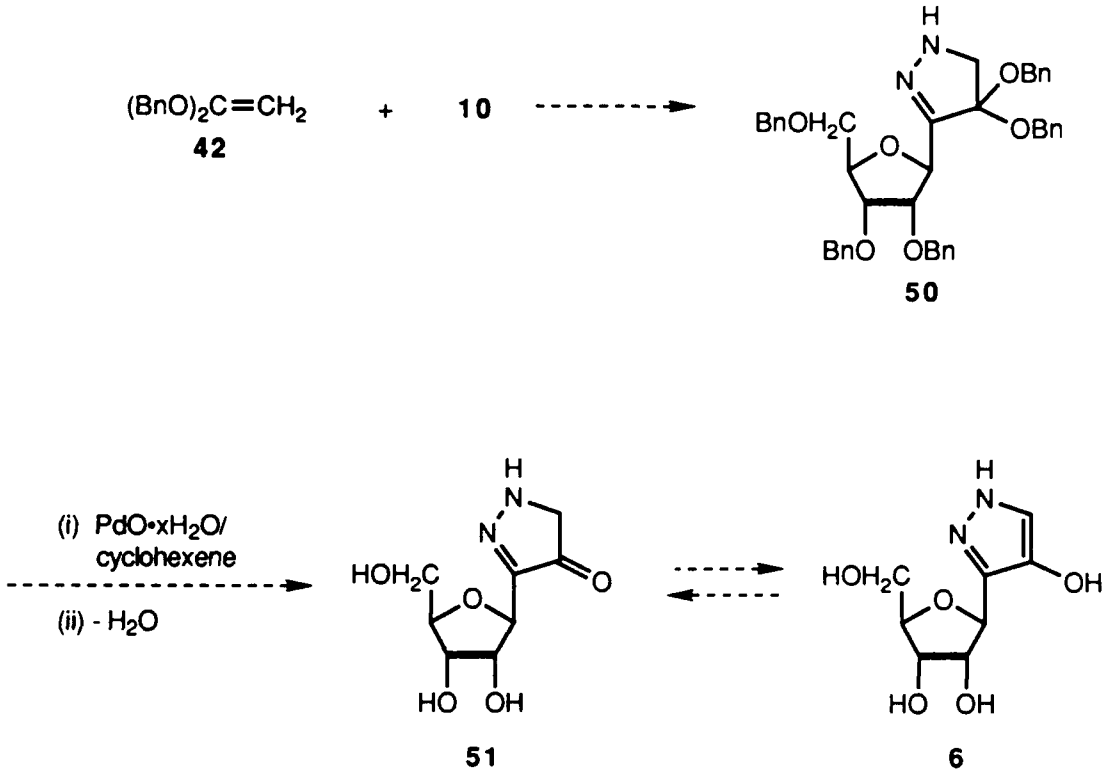




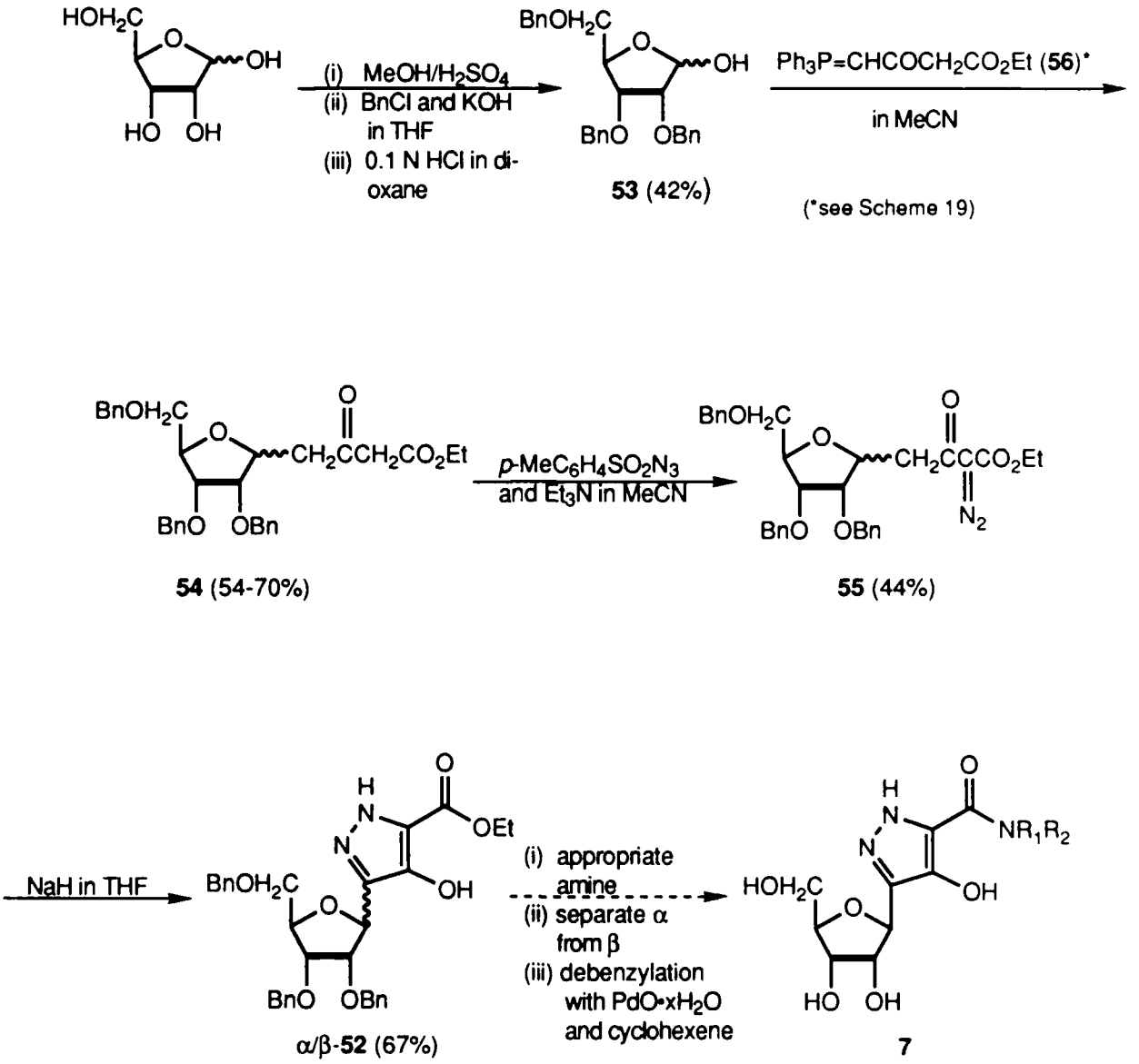
Possible mechanism for last reaction:



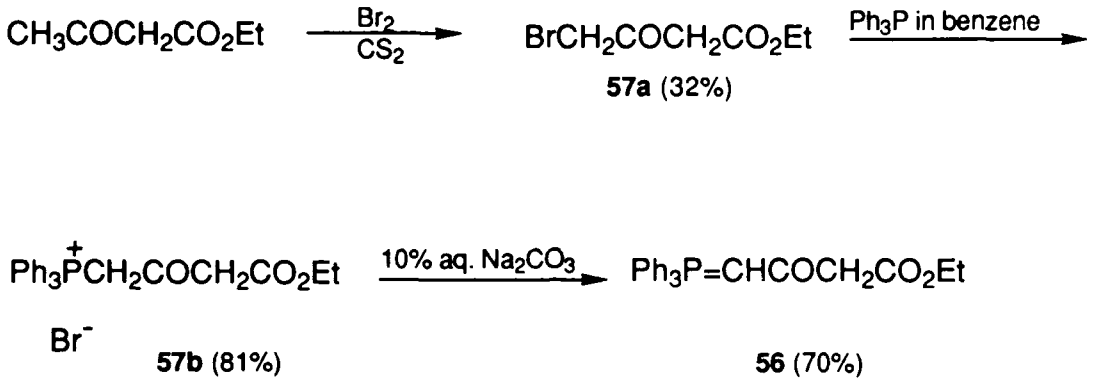
Scheme 17
Alternative Synthesis of **6**



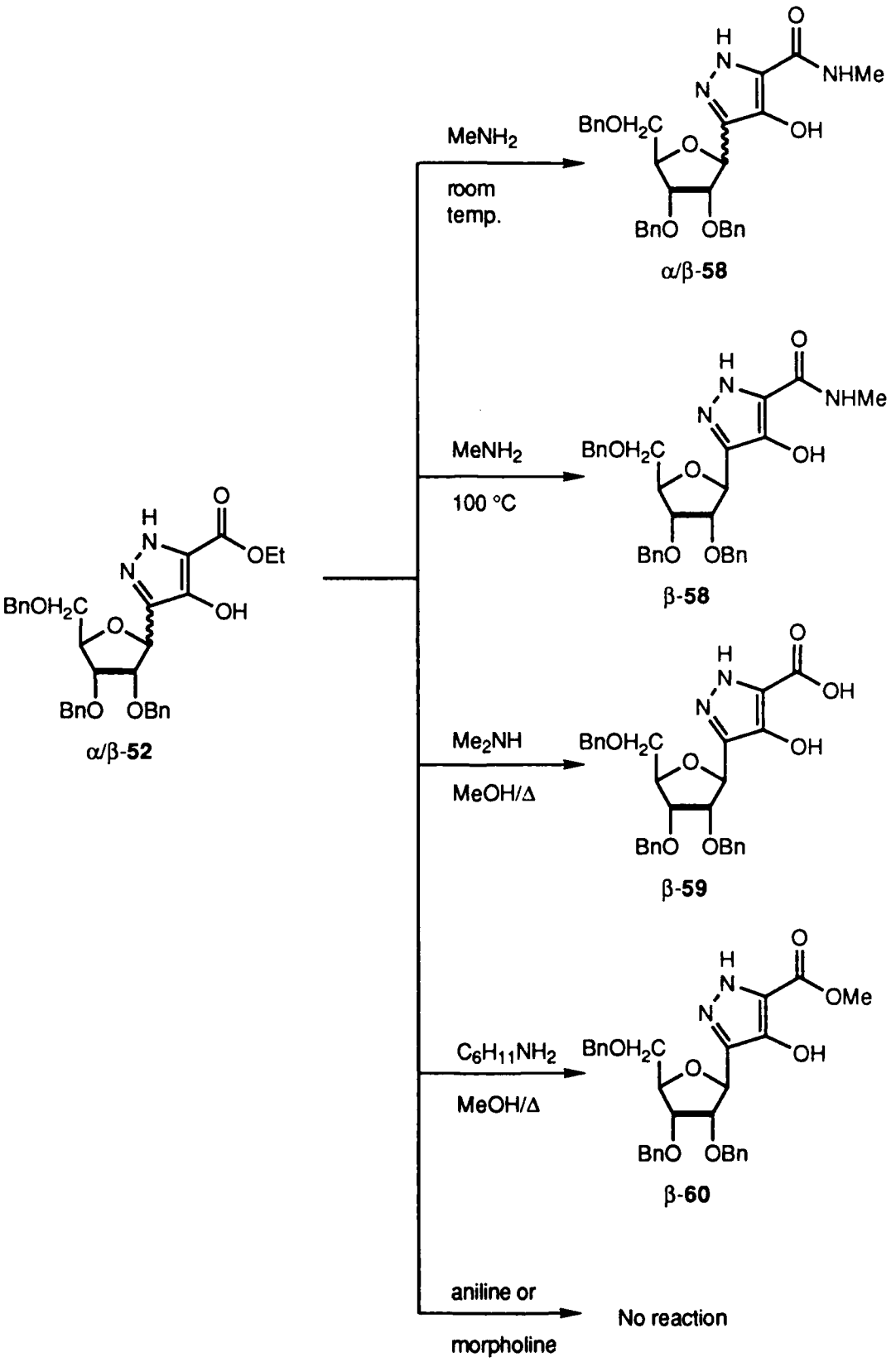
Scheme 18
Synthetic Approach to Pyrazofurin Amides (**7**)



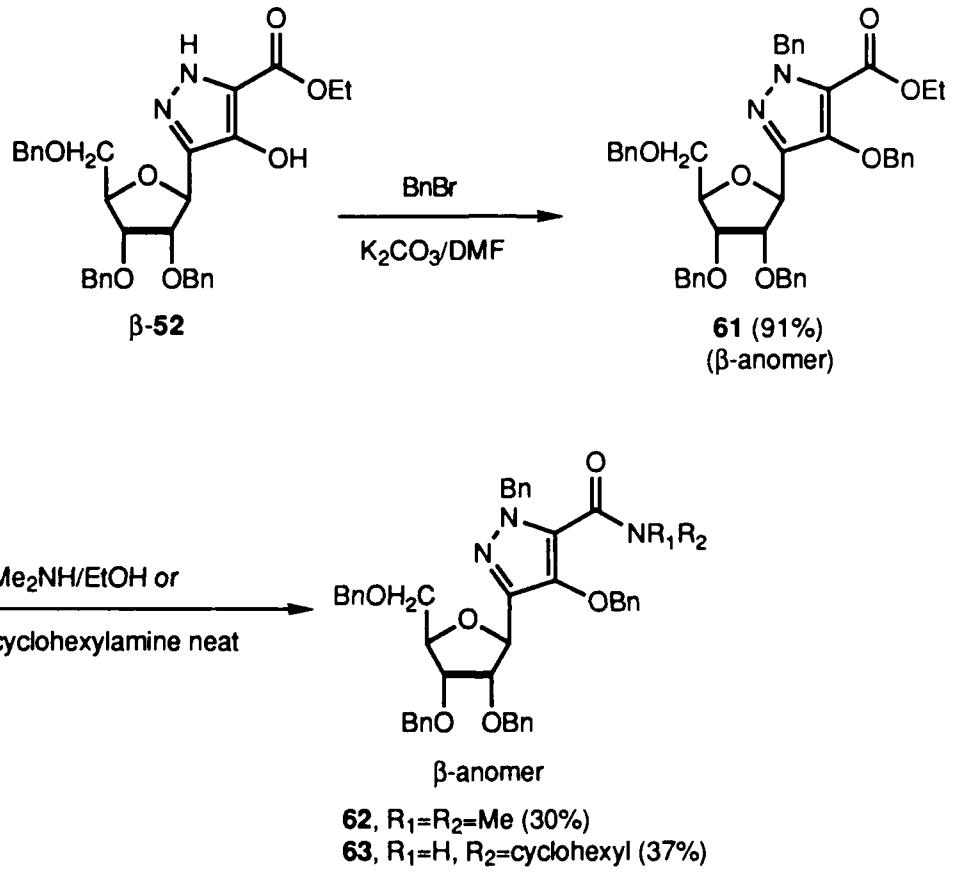
Scheme 19
Synthesis of the Wittig Reagent for Scheme 18



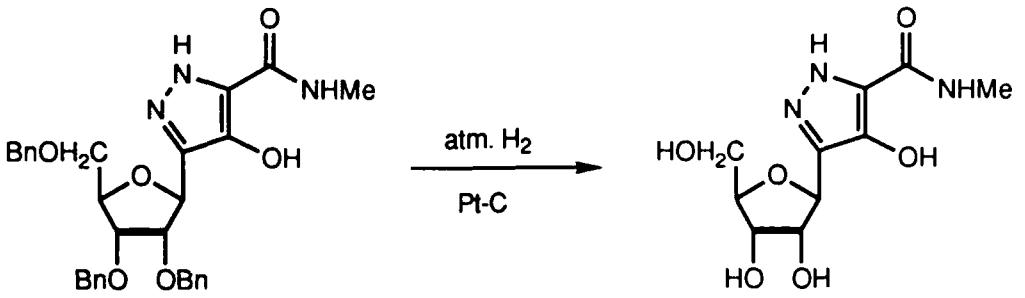
Scheme 20
Studies Toward Amide Derivatives (**7**)



Scheme 21
Preparation and Reactions of Benzylated Ester **57**



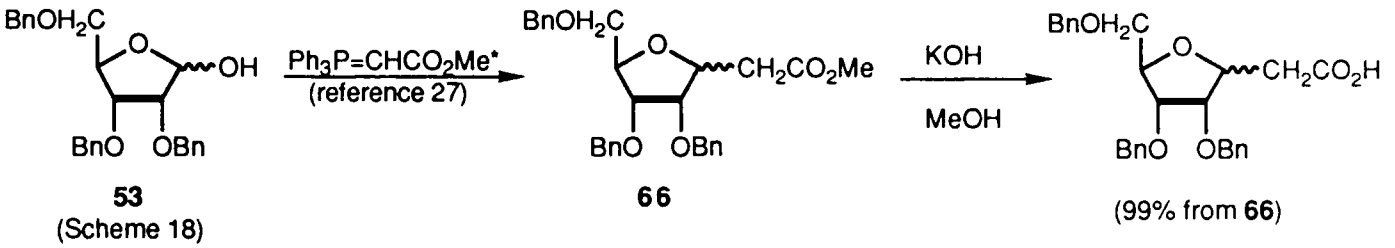
Scheme 22
Preparation of a Target Amide **7a**



β-**58**
(Scheme 20)

7a

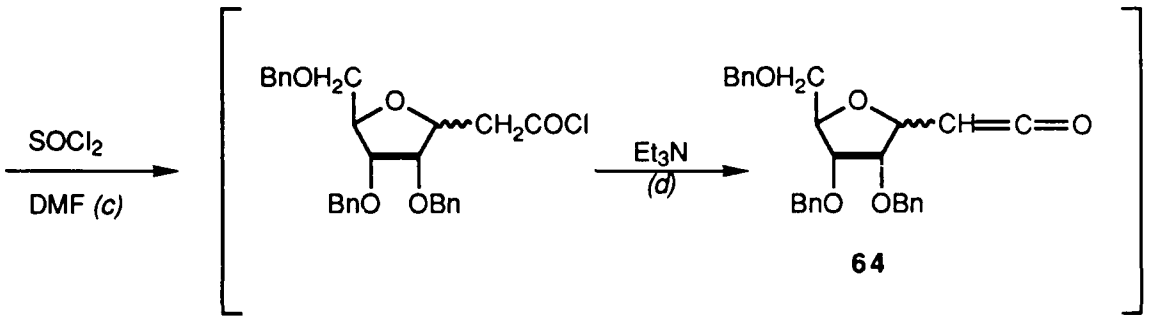
Scheme 23
Initial Approach to 2-Deazapyrazofurin (**8**)



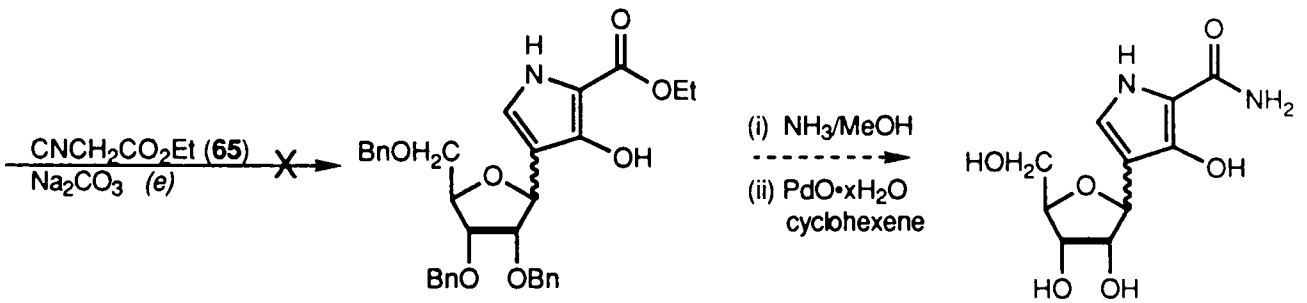
53
(Scheme 18)

66

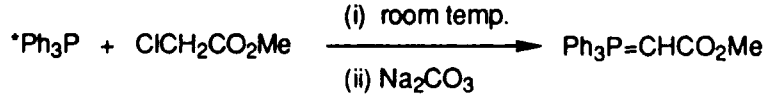
(99% from **66**)



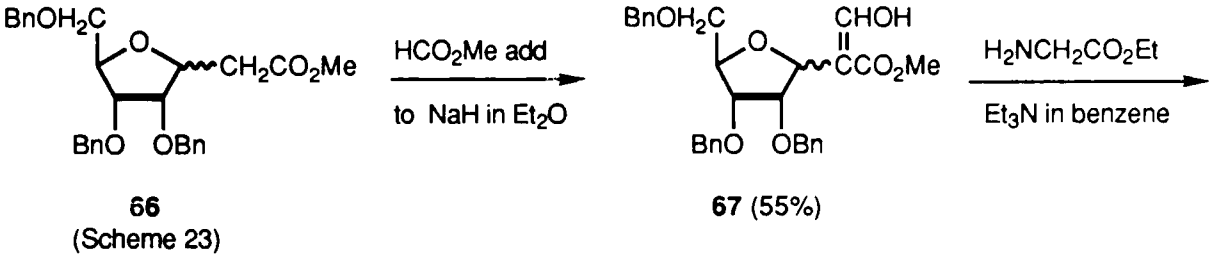
64



8

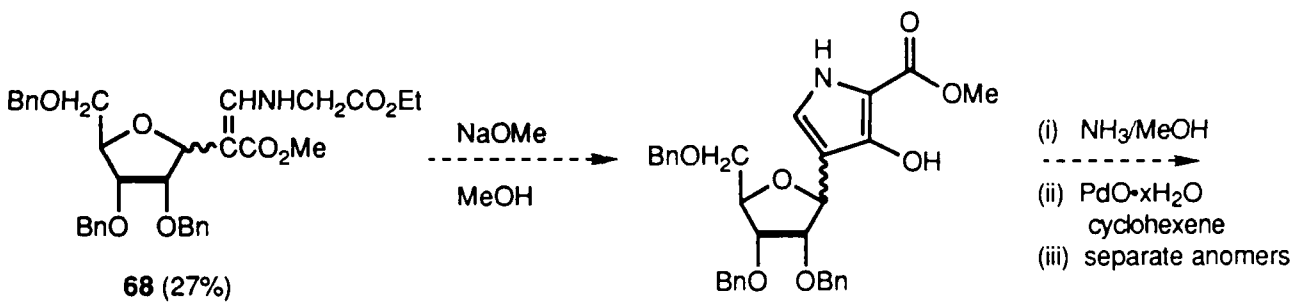


Scheme 24
First Alternative Approach to 2-Deazapyrazofurin (**8**)

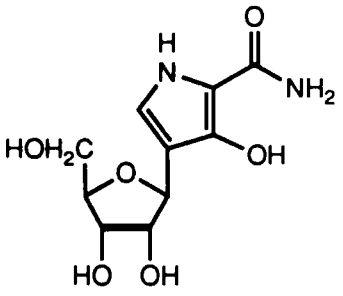


66
(Scheme 23)

67 (55%)

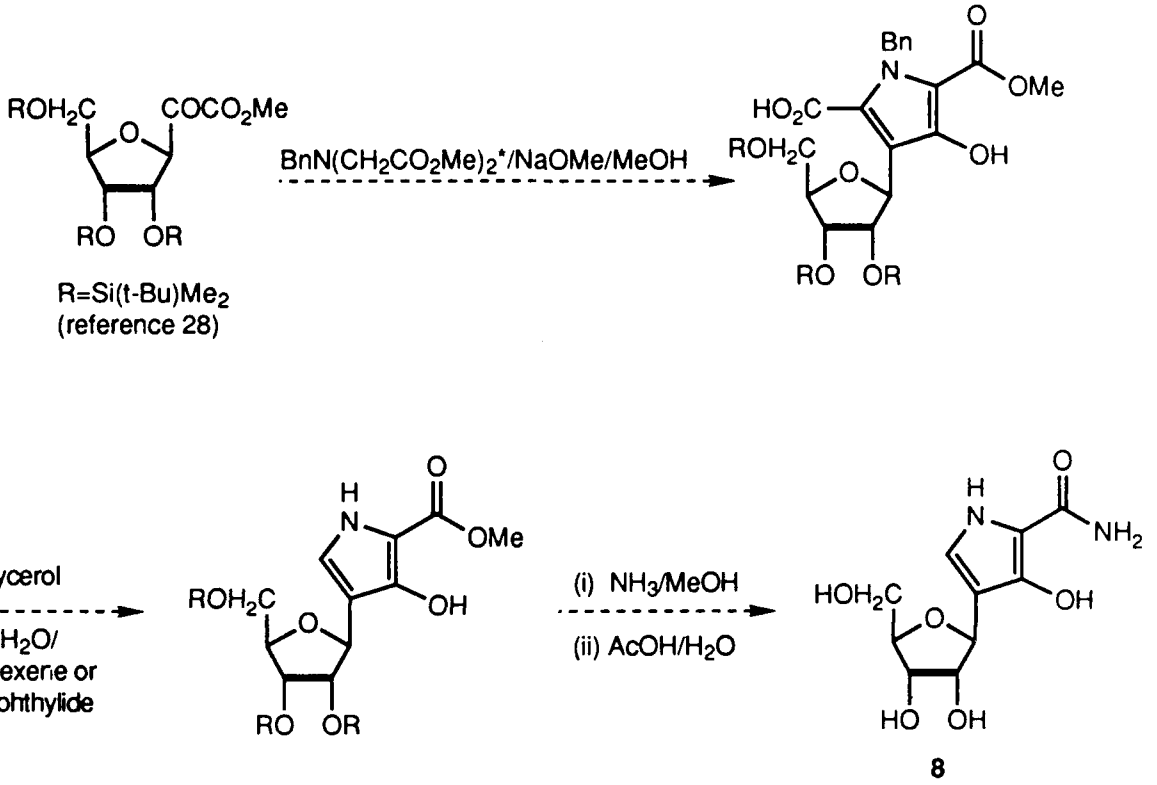


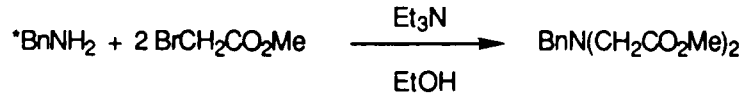
68 (27%)



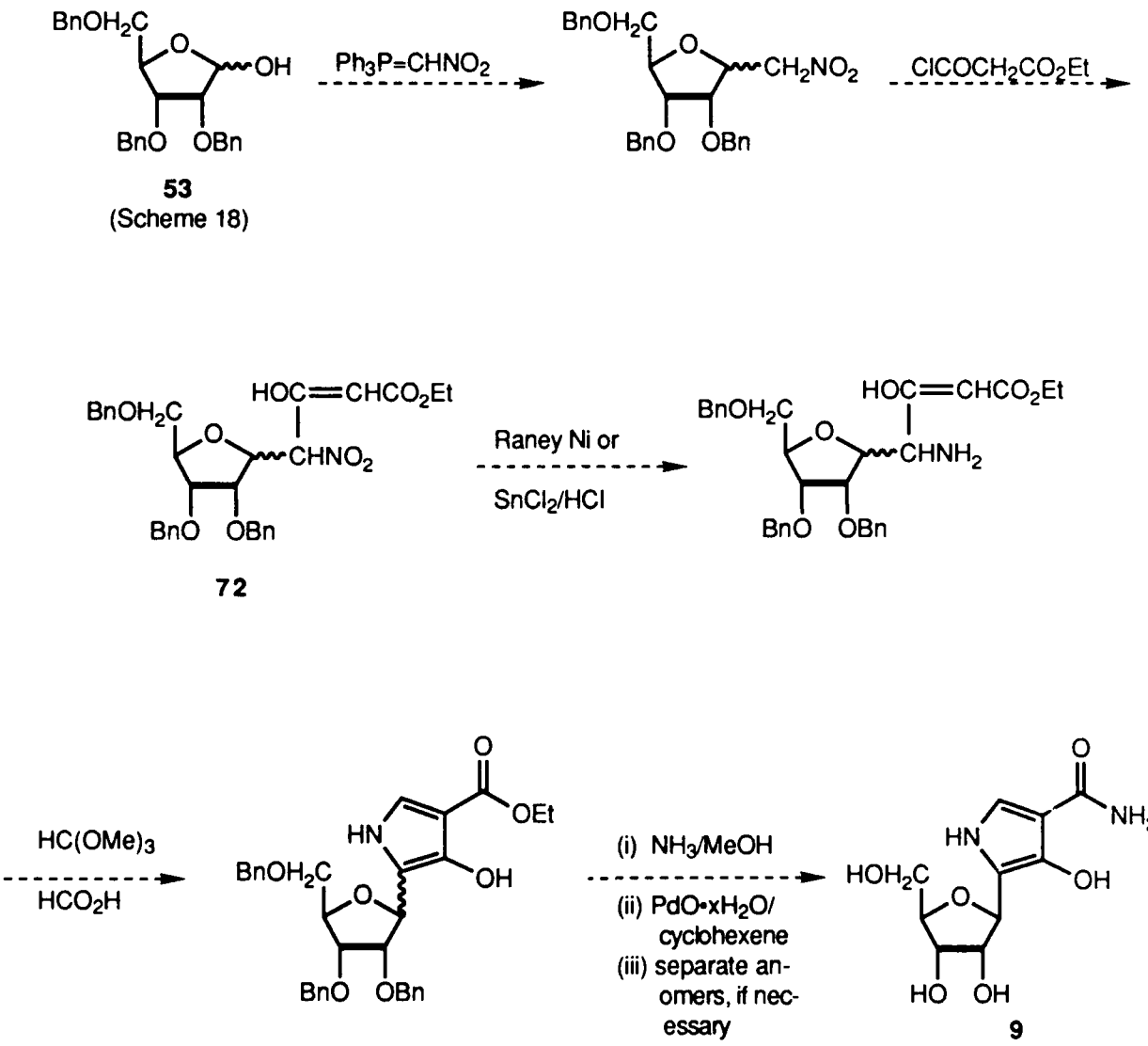
8

Scheme 25
Second Alternative Approach to 2-Deazapyrazofurin (**8**)





Scheme 26
First Approach to 1-Deazapyrazofurin (**9**)

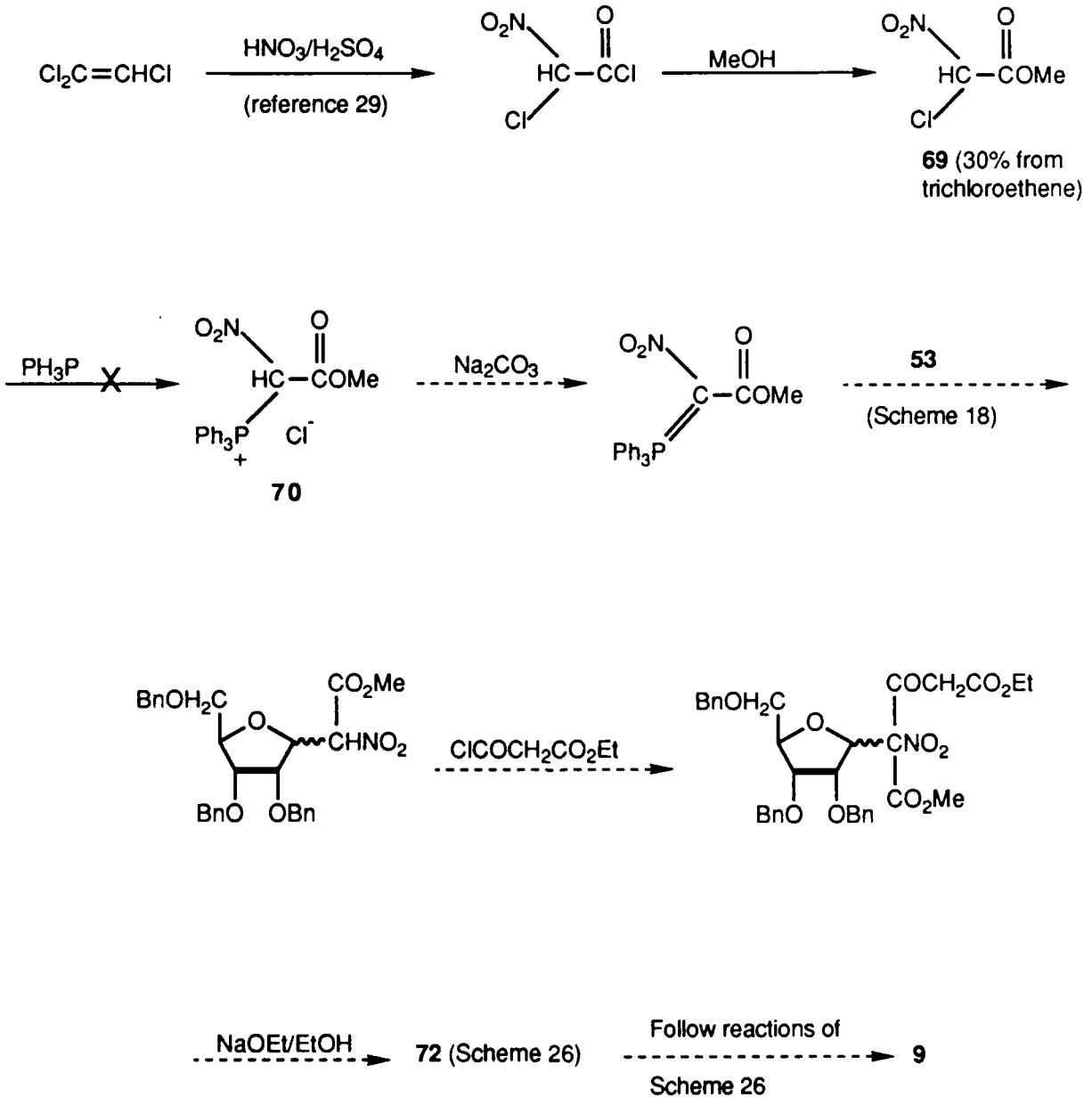


53
(Scheme 18)

72

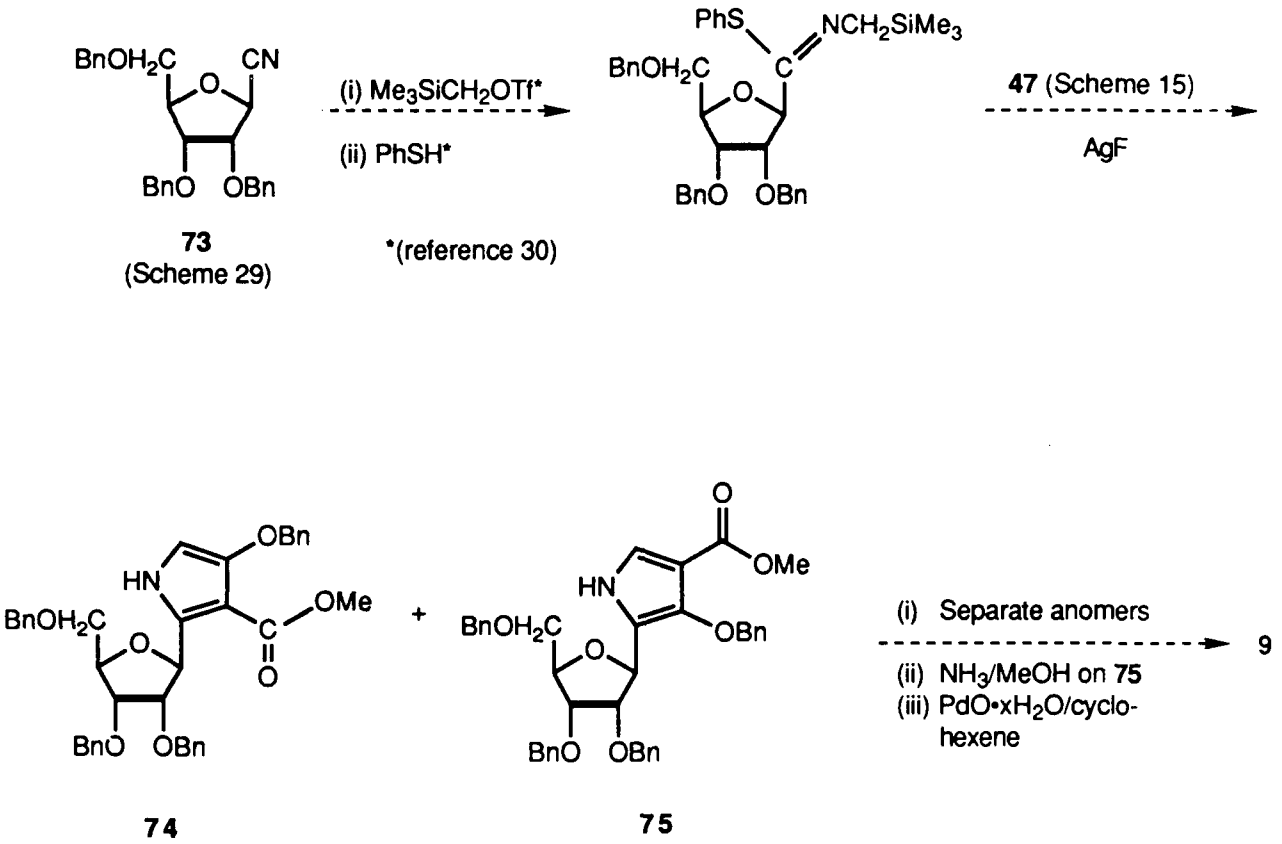
9

Scheme 27
Second Approach to 1-Deazapyrazofurin (**9**)

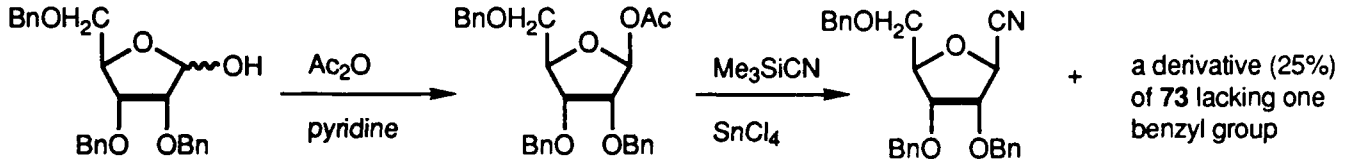


Scheme 28

Planned Approach to the Synthesis of 1-Deazapyrazofurin (**9**)



Scheme 29
Preparation of **73** Accomplished This Year

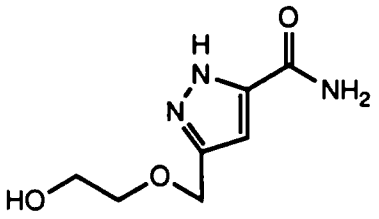
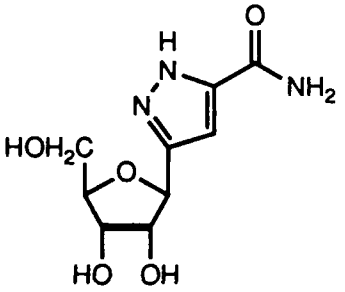
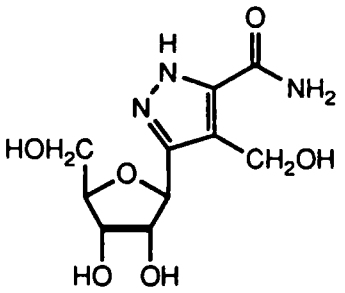
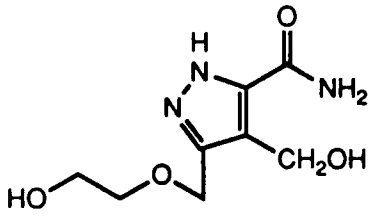


53
(Scheme 18)

76 (77%)

73 (34%)

COMPOUNDS SUBMITTED TO THE ARMY DURING THE REPORTING PERIOD

Structure	AVS Number	Contractor's Number	Reference to Synthesis*	Amount Submitted
	None assigned yet	PF-1 (DRS-II-164)	3	100 mg
	006973	PF-3 (DRS-II-200)	2	62 mg
	006974	PF-4 (DRS-II-208)	4	80 mg
	006950	PF-2 (DRS-II-184)	5	74 mg

*All syntheses are presented in this report; numbers in this column refer to the compound number for this analogue in the report to aid in locating the experimental details for its preparation.

PUBLICATIONS SUPPORTED BY THE CONTRACT

1. Sauer, D.R.; Schneller, S.W. "The Synthesis of 3(5)-[(2-Hydroxyethoxy)methyl]pyrazole-5(3)-carboxamide, An Acyclic Analogue of 4-Deoxypyrazofurin," *J. Org. Chem.* , in press

2. Sauer, D.R.; Schneller, S.W. "A Convenient Synthesis of 4-Deoxypyrazofurin," submitted to *J. Org. Chem.*

3. Sauer, D.R.; Schneller, S.W. "The Preparation of 3(5)-(β-D-ribofuranosyl)-4-(hydroxymethyl)pyrazole-5(3)-carboxamide (4-Homopyrazofurin) and Its Acyclic Analogue," to be submitted to *J. Org. Chem.*

PROFESSIONAL PRESENTATIONS SUPPORTED BY THE CONTRACT

1. "The Synthesis of 3(5)-Carbamoyl-5(3)-[(2-Hydroxyethoxy)methyl]pyrazole, An Acyclic Analogue of 4-Deoxypyrazofurin," D.R. Sauer and S.W. Schneller, presented at the 199th meeting of the American Chemical Society, April 22-27, 1990, Boston, MA

PERSONNNEL RECEIVING CONTRACT SUPPORT

Name	Category	Degree Received
Daryl Sauer	Graduate Student	PhD, April 1990
Linda Morgan	Technician	Not applicable
Purna Pradhan	Postdoctoral	Not applicable
Xing Chen	Postdoctoral	Not applicable